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The Journal of Laboratory and Clinical Medicine

A Monthly Journal Devoted to the Laboratory in its Relation to Medicine and Surgery

VICTOR C. VAUGHAN, M.D.,
Editor-in-Chief

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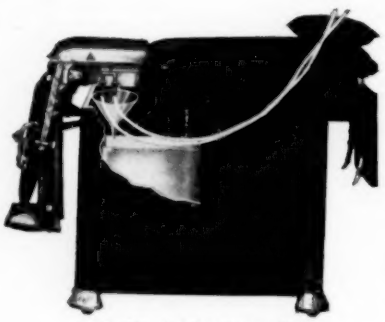

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The Journal of Laboratory and Clinical Medicine

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ORIGINAL ARTICLES

A NEW METHOD FOR THE PRODUCTION OF GENERAL ANALGESIA AND ANÆSTHESIA WITH A DESCRIPTION OF THE APPARATUS USED[1]

BY D. E. JACKSON, M.D., PH.D., ST. LOUIS, MO.

IN the following paragraphs there will be described a method for the production and maintenance of prolonged general analgesia or anæthesia by means of nitrous oxide, ethyl chloride, ether, chloroform, ethyl bromide, "somnoform," etc., with oxygen. The method involves a continuous process of rebreathing of the gaseous or volatilized anæsthetics from which the exhaled carbon dioxide, etc., have been removed and to which oxygen is constantly added in proportions suitable to maintain the patient in a satisfactory condition. The method involves the use of special apparatus which is so arranged as to give the anæsthetist complete control of every phase of the anæsthesia at all times. In the apparatus here described great care has been taken to provide safety devices. So far I have had an opportunity to try this method only on animals, but there seems to be good reason to expect that in man results entirely comparable to those produced in animals may be readily obtainable. It is chiefly with this object in view that I have carried out a long series of experiments by this method.

A number of the basic principles upon which I have constructed the apparatus herein described have long been known to science. As early as the year 1780 Antoine-Laurent Lavoisier had isolated carbon dioxide from expired air and had shown that in respiration oxygen is consumed, thereby starting work which within the next century was to lead to a long series of brilliant investigations along the lines of general metabolism and of analysis of respired gases. Names which should perhaps here be mentioned in connection with this subject are, Magnus (1837), Bischoff (1837), Regnault and Rieset (1849), Voit (1861), Pettenkofer (1863), Andrews (1868), Pflüger (1868), Bert (1878), Zuntz (1880), C. Martin (1888), Geppert and Zuntz (1888), Luciani and Piut-

[1]From the Department of Pharmacology, Washington University Medical School, St. Louis, Mo.

ti (1888), Atwater and Rosa (1899), Hewitt (1900), Haldane and Pembrey (1900), Atwater and Benedict (1905), Cushny (1909), Benedict (1909, 1912), Rolly and Rosiewicz (1911), Yandell Henderson (1910), Gatch (1911), and Meltzer and Auer (1909-11). Regnault and Rieset were probably the first to pass a current of oxygen into a small chamber in which an animal was confined for the purpose of analyzing the changes produced in the air by the respiration of the animal. They used a strong alkaline hydroxide solution to absorb the carbon dioxide output of the animal. Oxygen was added from a constant pressure reservoir. These principles have been used by practically all workers on respiratory metabolism since 1849. In the present experiments I have utilized them not for the purpose of obtaining data regarding the metabolism of the animal but with the object of maintaining conditions suitable for the normal respiration of the animal while at the same time there are added to the respiratory medium such quantities of gaseous or volatile anæsthetics as may be necessary to produce and maintain any desired and attainable degree of analgesia or anæsthesia, depending on the pharmacological properties of the substance administered. It will be noted at once that only very small quantities of the anæsthetic, such as nitrous oxide, ethyl chloride, ether, ethyl bromide, etc., are needed to produce a prolonged effect on the animal. And the depth of the anæsthesia becomes simply a matter of the degree of saturation of the animal with the anæsthetic. Since the anæsthetist has complete control of the amount of anæsthetic introduced into the animal it is obvious that when the desired degree of nervous depression has been reached no more anæsthetic need be given. The method by which these results are attained can best be explained by reference to Fig. 1 which is a diagrammatic plan of the apparatus used.

Description of Apparatus

A small electric motor (1) operates an air pump (2) which may be either of the rotary form (as shown here) or, perhaps, better of the piston form. By means of a closed system of pipes and vessels air may be kept continually circulating through the apparatus without either loss or gain of air except at the instance of the operator. Air leaving the pump at pipe (3) passes by the valve (4) unless this valve be open in which case part or all of the air will escape into the room. If the valve (4) be closed then the air proceeds through the valve (5) past the air-cock (6) and through pipe (7) into the special wash jar (9). This jar is three and one-half inches in diameter and twelve inches high and has an air-tight cover. The glass tube entering the jar is connected with the outer metal pipe by rubber hose. The glass tube makes an S-shaped bend a little distance below the cover and then passes through a bell-shaped piece of glass (8) which is firmly attached to the glass tube. Below the glass bell the tube again passes down inside a glass cylinder about two inches in diameter and six inches long. This cylinder reaches nearly to the bottom of the jar and is firmly attached to the glass tube by four glass spokes, two above and two below, each pair of spokes being placed in the same straight line, but on opposite sides of the glass tube. The glass tube lacks about one inch of reaching as low down as the outer glass cylinder. The jar is filled to the height of three or four inches from the bottom with a strong aqueous solution of sodium hydrate and calcium hydrate. The purpose of this solution is to absorb the

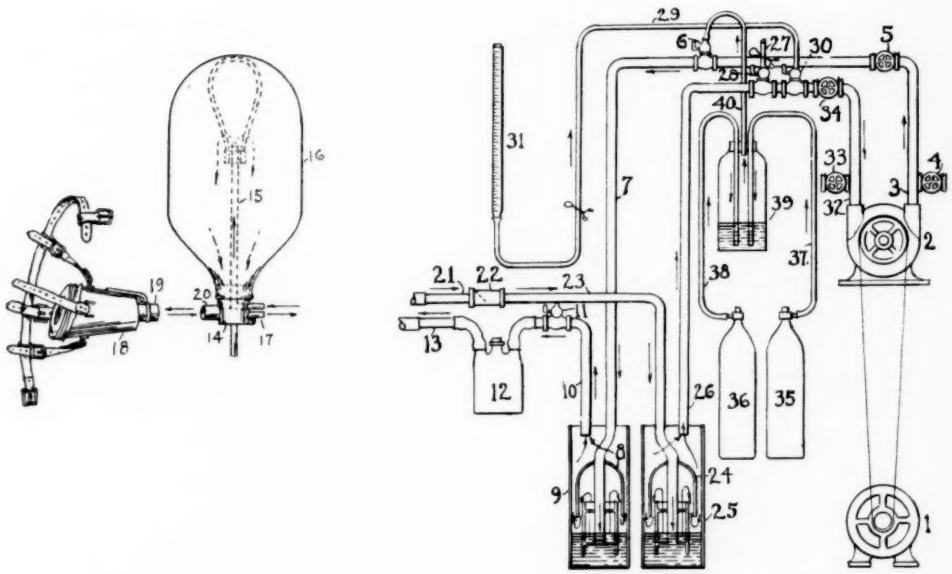

Fig. 1.—Schema showing the general plan of the apparatus together with head-piece, breathing bag and muzzle, as arranged for use with animals. The arrows indicate the direction of the air current. Number 35 represents the oxygen tank and 36 the nitrous oxide tank. In reality the apparatus carries two tanks each of oxygen and nitrous oxide. For full description see text.

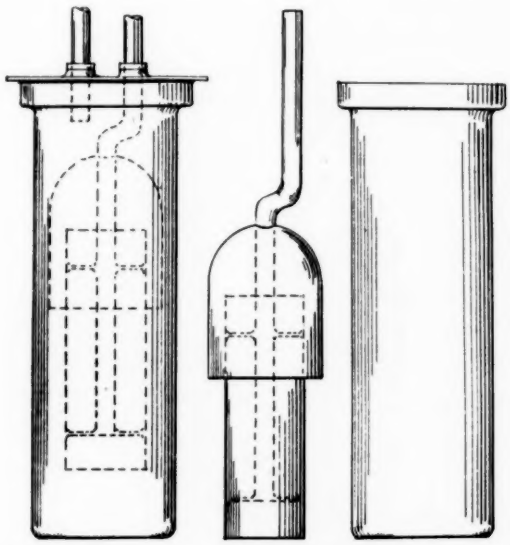

Fig. 2.—This drawing illustrates on an enlarged scale the wash jars shown at 9 and 25 in Fig. 1. For use the jars are filled with fluid to the height of 3 or 4 inches. For full description see text.

carbon dioxide produced by the animal. Air entering through the glass tube passes out of the lower end of the tube into the solution. Since there is a strong current of air circulating there is a great deal of splashing of the fluid. But this splashing is almost wholly confined within the glass cylinder. This upward splashing is entirely caught by the glass bell and directed back down into the jar. The air passes up into the bell, thence downward underneath the lower edge of the bell, thence upward into the upper part of the jar and out through

the tube (10) which leads past an air-cock (11) into a glass chamber (three-necked Woulff bottle) which serves as a safety device permitting the operator to see if any fluid, etc., is passing from the machine to the animal. In this reservoir (12) may also be placed water to moisten the air breathed (I have not found this to be necessary), sodium bicarbonate solution to further purify the air (I have not found this to be necessary), or, carbon dioxide or other drugs or gases may be introduced into it especially for experimental purposes, or, oil of bitter orange peel may be placed in it to perfume the air breathed by the patient. From this reservoir the air passes through the pipe (13) to which is connected an ordinary red antimony rubber hose about three or four feet long and having an inside diameter of three-eighths of an inch. This hose carries the air (and anæsthetic) to the face- (or head-) piece. Two special forms of face- (or head-) pieces have been made, one for dogs, the other for man. I shall confine the description mainly to the former since I wish to deal only with animal experiments in this paper.

In the animal head-piece a tapering brass cylinder about two inches in diameter at the top is closed at the bottom (14). Fastened to the bottom is a brass rod which extends downward about two and one-half inches. This rod may be inserted into a hole in the operating board and thus serve to hold the head-piece upright. Into the right-hand side of the cylinder are soldered two brass tubes three-eighths of an inch in diameter. To the outer ends of these are attached the rubber hoses passing to and from the machine. The brass tube carrying air into the cylinder turns upward at a right angle near the center of the cylinder and thus carries the air up near the top of the surrounding rubber bag. To the upper end of this tube it attached (by each end) a long coil of steel wire which forms a closed loop above the tube and serves as a flexible support for the rubber bag (16) which is slipped down over the spring. (The sides of the spring are bent in close together for removing or replacing the bag.) The lower end of the rubber bag fits snugly around the upper end of the brass cylinder. In the left side of the brass cylinder is an opening into which is soldered a brass tube (20) about one and one-eighth of an inch in diameter and about three-fourths of an inch long. The animal breathes back and forth through this tube. A large perforated cork may be placed in this tube and the side tube of a tracheal cannula slipped through the hole in the cork if one cares to open the trachea. If one does not desire to kill the animal then the metallic muzzle (18) as shown in the diagram may be placed over the animal's nose and mouth. This muzzle is a brass cylinder tapering toward the front where it ends in a large opening into which a flange (19) is soldered. This flange slips over the tube (20) on the head-piece, the joint being made air-tight by a broad rubber band. The rear end of the muzzle is slanted at an angle as shown in the diagram, and around the edges on the outside are soldered two rings of heavy wire. A sheet of heavy rubber dam is tied over the rear end, a number 18 wire being used to tie the rubber down in between the two heavy wires soldered to the rim of the muzzle. In the center of the rubber dam a round opening about one and one-eighth inches in diameter is made. This slips tightly over the animal's nose and mouth. The muzzle is held on by four straps which pass to a collar to which each is attached by buckles. I have found this muzzle fairly satisfactory. The objections are that the animal cannot open its

mouth well to breathe and saliva is liable to occasionally accumulate within the muzzle. The first objection is liable to be noticed with nitrous oxide, and the latter with irritating anæsthetics.

Within the head-piece and rubber bag a thorough ventilation of the air is assured by having the incoming air pass in near the top of the bag while

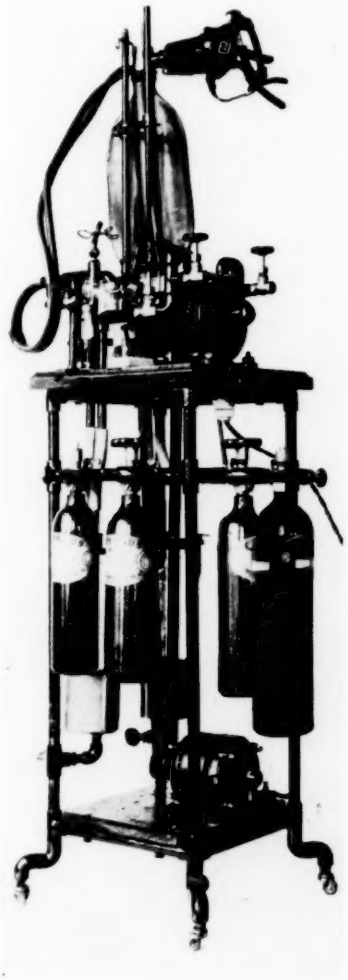

FIG. 3.

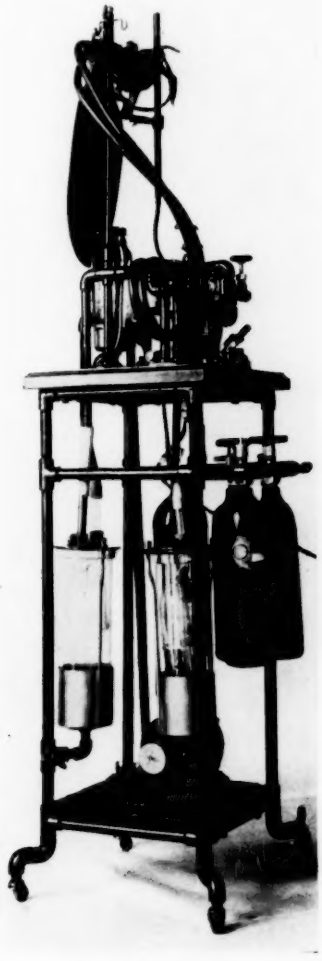

FIG. 4.

Fig. 3.—General view of the apparatus showing the left and rear sides. The muzzle, head-piece and breathing bag as arranged for dogs are shown hanging from a hook at the top of the apparatus. The rubber tubes connecting the head-piece to the apparatus are three or four feet long, thus enabling the anæsthetist to place the apparatus at a considerable distance from the animal when an anæsthetic is being given.

Fig. 4.—General view of the apparatus showing the front and left sides. The position of the wash jars is well shown.

the outlet is at the bottom. This occurs only while the pump is running. If the pump be stopped any desired amount of rebreathing may be secured. Oxygen may be allowed to reach the bag constantly or intermittently as preferred so the oxygen supply to the animal is entirely independent of the rebreathing or

of the carbon dioxide content of the bag. (These same principles apply in the face-piece which I have constructed for the human subject.) From the head-piece air passes out through the rubber hose at (17) and back to the machine with which it is connected by the metal pipe (21). These two pieces of rubber hose are clamped side by side by small flat metal clamps. They are thus

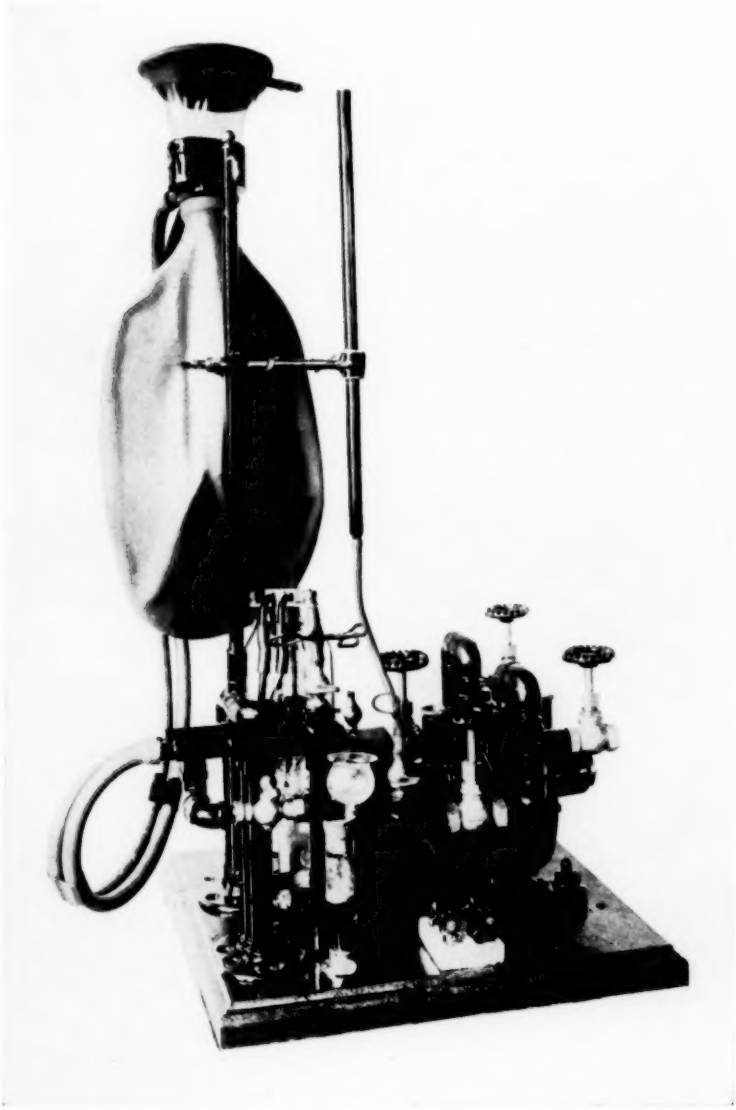

Fig. 5.—View showing the upper portion of the apparatus. The breathing bag and face-piece as arranged for man are shown hanging from a hook at the top of the apparatus.

kept almost entirely out of the way. This head-piece may also be used for intra-tracheal insufflation. The tube leading to the head-piece in this case has a Y-tube inserted in its course near the brass cylinder of the head-piece. From the two forks of the Y-tube short rubber tubes carrying screw clamps pass to the cylinder. One of these tubes connects onto the inlet tube as usual. The

other rubber tube is connected with the inside of the cylinder by means of a small metal or glass tube passing through a cork inserted in an opening in the brass cylinder (not shown in the diagram). From this small tube inside the cylinder a catheter may be passed out through the flange (20) and either enter the trachea directly or pass in at the side tube of a tracheal cannula. The correct amount of pressure for the intra-tracheal tube can be obtained by adjusting the screw clamps on the short rubber tubes coming from the Y-tube. (I believe this same principle may very well be used in man, possibly even for nitrous oxide anæsthesia).

Air passing from the animal back to the machine enters the pipe (21) and soon reaches a check valve (22) which is intended as a safety device to pre-

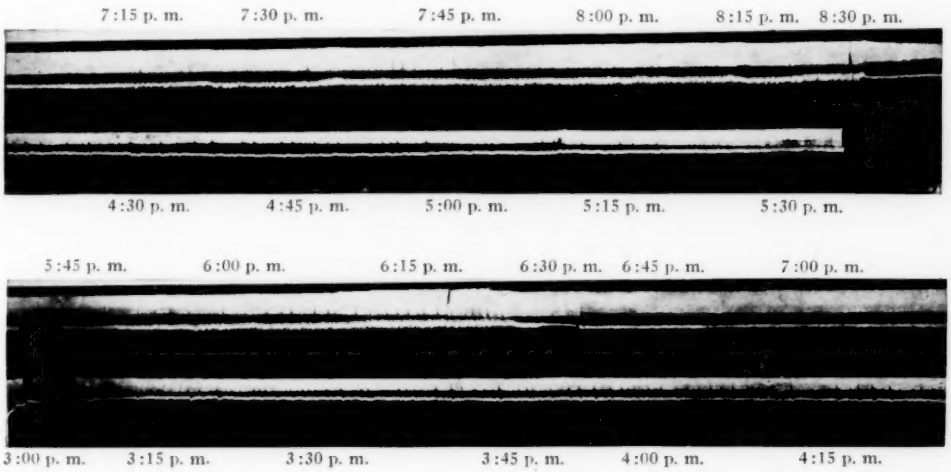

Fig. 6.—This is a photographic reproduction (in two sections) of the blood pressure and respiratory tracings from a dog under *nitrous oxide* anæsthesia. The original tracing formed a single record eighteen feet long as recorded on a slowly moving drum. The total length of duration of the anæsthesia was a little more than *five and one-half hours* and the animal was in excellent condition at the close of the experiment. The time is marked on these records in fifteen-minute intervals. A few breaks in the course of the tracings are due to clots in the arterial cannula, readjustment of the apparatus, etc. The signal magnet (at the base line) shows five-second intervals.

vent any reversal of the air current. From this valve the air passes through the pipe (23) to a second wash jar (25) exactly like the first but containing concentrated sulphuric acid which removes excess moisture from the air. This acid also serves the further purpose of being a good sterilizer of the air leaving the animal's lungs. And the faint possibility of any organic poison being exhaled by the animal is also provided against by the acid. In addition, by placing the acid here, the air which passes on to the pump is made relatively dry and this serves to prevent the pump from rusting.

From the wash jar (25) the air passes through the pipe (26) back toward the pump. But at a short distance from the pump two air-cocks are connected with the tube. Through the first of these cocks (28) such volatile substances as ethyl chloride (kelene), ethyl bromide, somnoform, etc., may be sprayed into the machine through a short piece of rubber tubing carrying a clip (27). Still nearer the pump is another air-cock (30) through which less volatile substances such as ether or chloroform (or ethyl bromide) may be injected from a burette (31). This permits of very accurate dosage, but in this connection

one must remember that it is necessary to saturate the air and solutions in the machine to a certain definite degree in order to secure and maintain any definite degree of anæsthesia in the animal. This can be done, however, approximately at least, by injecting some ether, etc., into the machine and running the

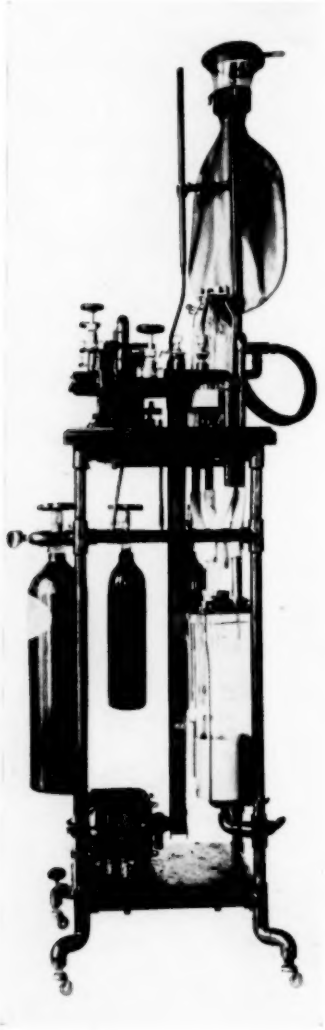

Fig. 7.—General view of the right-hand side of the apparatus. The face-piece and breathing bag as arranged for man are shown at the top of the apparatus. Just to the left of the bag is shown a twenty-five cubic centimetre burette (graduated to tenths of a c.c.) used for the injection of ether, chloroform, etc., into the air system.

pump for a little time before the machine is connected to the animal. It is advisable to do this also with nitrous oxide.

Still nearer to the pump is another valve (34) which is placed in the main air circuit. This valve corresponds with the valve (5) which is also placed in the main air circuit. Valve (33) opens to the outside air. If, while the pump is running, valve (4) be slightly opened a little air will be forced out of the system into the room. This will instantly reduce the quantity of air in the re-

spiratory bag. By watching the bag as one opens the valve (4) cautiously the tension of the air in the bag can be immediately reduced to any desired degree. Conversely by slightly opening valve (33) any desired quantity of air can be drawn into the system. These two valves give the operator complete control at all times of the amount of air in the machine and these adjustments can be made in a few seconds. Through pipe (32) the air current again enters the pump and passes out through pipe (3). This completes the circuit of the air which has lost some of its oxygen to the animal but has gained some carbon dioxide and watery vapor. The carbon dioxide in the next few rounds will be taken up by the soda-lime while the watery vapor will be taken up by the sulphuric acid. The oxygen, however, must be replaced from the outside. This is accomplished by injecting oxygen from an ordinary commercial oxygen tank (35) into the air circuit. From the tank a tube (37) leads to a wash bottle (39) containing water or sodium bicarbonate solution through which the oxygen passes. From the top of this wash bottle a tube leads to the air-cock (6) through which the oxygen is passed into the air system. The extent of distension of the bag and the symptoms of the animal serve as guides for the administration of oxygen.

Nitrous oxide may also be administered in the same manner as the oxygen as shown in the diagram. Carbon dioxide may also be injected into the system from an ordinary commercial tank of the gas by way of the air-cock (11) just in front of the reservoir (12). Number 36 represents a tank of N_2O.

Theoretical Discussion

It is obvious at a glance that no anæsthetic can be used in this machine which will undergo decomposition or be chemically changed by contact with concentrated sulphuric acid or sodium or calcium hydrate solution. By a peculiarly fortunate coincidence sulphuric acid and sodium hydrate solution are the two most common reagents used in the purification of a majority of the anæsthetics in general use. And in this machine the anæsthetic undergoes a constant purification. I have suspected this might be of some real benefit practically. So far I have successfully used nitrous oxide, ether, chloroform, ethyl chloride, ethyl bromide,[2] and the proprietary preparation "somnoform." While my original object was mainly the production of a method by which nitrous oxide anæsthesia might be made cheaper and safer, thereby extending its use particularly to that large and unfortunate proportion of our population which must depend on charity for its surgery, I am now inclined to believe that the method may well be used for a majority of the anæsthetic substances now known.

It is one of the basic principles of pharmacology that most anæsthetic substances which are administered through the lungs by inhalation are almost totally excreted again by exhalation from the lungs. Such small quantities of the common anæsthetics as might disappear in the tissues would probably have no influence whatever on the use of this method. By means of the constant circulation of the air within the machine the exhaled anæsthetic is simply carried around, washed through the sulphuric acid and sodium hydrate solution and again returned to the animal for rebreathing. It is thus seen that so long

[2]Ethyl bromide "is with much difficulty saponified by potassium hydroxide and it is not attacked by sulphuric or nitric acids" (New and Nonofficial Remedies, 1915, p. 26). I have not experienced any difficulty in this direction in the use of ethyl bromide.

as no air is allowed to enter the machine from without and none is allowed to escape from within, the concentration of any given anæsthetic vapor within the machine and in the tissues of the animal must remain practically constant. Consequently the degree of anæsthesia should also remain constant. It is easy enough to carry this out with such a substance as ether. But it is somewhat more difficult with the milder anæsthetics such as nitrous oxide or ethyl chloride. With these bodies it is often difficult for one to interpret the degree of analgesia or anæsthesia present *in dogs*. I suspect it might be easier to do this in man. In dogs under ethyl bromide it may sometimes be found, for exampie, that touching the cornea will not cause winking and yet the animal may struggle about rather violently entirely independently of the carbon dioxide or oxygen present, and when one may feel very sure that the animal is entirely unconscious of painful sensations. One is always tempted then to give more of the anæsthetic, but a slight increase in the concentration of the vapor may throw the animal into a dangerous condition. It would seem probable in such cases that the drug may have been performing its full therapeutic function as an analgesic and if one could control the struggling this analgesia might easily be maintained for a prolonged period. I suspect that, particularly with ethyl chloride, this might be done in the human subject (e. g., in obstetrics) very much more satisfactorily than with the dogs on which I have experimented. With ether, however, one can check the struggling at an early stage of the anæsthesia and by carefully injecting small quantities (½ to 1 c.c.) at a time the animal may be brought to a condition in which it will just wink the eye when the cornea is touched and yet the skeletal muscles will all be relaxed and no voluntary movements may occur. One may stop giving the anæsthetic at this point and then maintain this stage of anæsthesia for twenty or thirty minutes. But if the degree of saturation of the tissues of an animal with an anæsthetic remains constant then the animal will tend to gradually fall more and more under the influence of the drug.

It is neither necessary nor desirable that the pump be running continuously. It has been repeatedly and most excellently shown by Yandell Henderson that a moderate accumulation of carbon dioxide may be of decided benefit to an animal under anæsthesia. By simply stopping the pump in this machine one can allow any extent of rebreathing or of carbon dioxide accumulation he may desire. And during this period he may or may not give the animal oxygen as he sees fit. Or he may even give the animal carbon dioxide from a tank if he wishes to do so. On the other hand if one prefers he may keep the pump running all the time and thereby almost entirely prevent any carbon dioxide accumulation within the breathing bag.

It has been repeatedly shown that warmed vapors are more satisfactory for anæsthesia than those which are cold. This machine automatically warms all gases or vapors circulating through it to approximately room temperature. This is accomplished first by the sulphuric acid which becomes warm from the absorption of moisture and second by the pump which develops heat from its friction in turning and by compression of the air passing through it. The alkali solution usually remains at practically the same temperature as the room and this determines the temperature of the air as it passes into the bag. The bag should be large, perhaps about one and one-half or two times the vital

capacity of the animal (or even larger). I have tried several different bags. In every case I have found that the larger the bag is the better the results are. When the air reaches the bag, which is made of thin rubber and has a large surface, then the temperature of the air in the bag should soon reach almost exactly that of the surrounding atmosphere. In rebreathing the animal itself quickly warms the air in the bag.

The air breathed by the animal should be properly moistened (perhaps of between 50 and 70 per cent relative humidity). I have had no difficulty in this respect with the machine. But if desirable water may be placed in the reservoir (12) to moisten the air before it passes to the bag. Too much moisture in the air I believe can be satisfactorily provided against by increasing the quantity of sulphuric acid in the wash jar [or possibly by placing acid in the reservoir (12)].

I have, unfortunately, not been able so far to make any very careful *practical* determination of how much sodium (and calcium) hydrate may be required for this method of anæsthesia by the hour. The amount must necessarily vary greatly in different animals and with different anæsthetics. The cost of the oxygen will probably represent the chief expense of anæsthesia by this method. And this is determined by the amount of the gas *actually consumed* by the animal. The sulphuric acid may be purchased very cheaply and this expense cannot be great. It should be possible to calculate approximately the amount of hydroxide and of oxygen which would be required for an anæsthesia of any given length of duration. "In an average man weighing 70 kilos the mean production of carbon dioxide is about 800 grammes (400 litres) in twenty-four hours, and the mean consumption of oxygen about 700 grammes (490 litres)."[3] But there are very great variations depending upon the state of the body as regards rest or muscular activity, and on other circumstances. In hard work the production of carbon dioxide was found to rise to nearly 1,300 grammes, and in rest to sink to less than 700 grammes, the consumption of oxygen in the same circumstances increasing to nearly 1,100 grammes and diminishing to 600 grammes. In rest, in moderate exertion, and in hard work, the production of carbon dioxide was found to be nearly proportionate to the numbers 2, 3, and 6 respectively."[4]

The production of carbon dioxide in an animal under deep anæsthesia must be very much less than during conditions of normal activity. And a corresponding decrease in the consumption of oxygen also occurs under the anæsthetics. It is often striking to observe during an anæsthesia by this method how small a quantity of oxygen is really required in order to keep the circulation and respiration in good condition. Using the above data as given by Stewart I have made a rather unsatisfactory theoretical calculation which shows that the cost of nitrous oxide anæsthesia for a dog weighing 15 lbs. (1/10 the weight of an adult man) should be approximately $0.0399 per hour. I believe that I have used more material than this figure would indicate in my experimental observations, especially of oxygen and sodium hydrate. The nitrous

[3]It will require 1,455 grammes (3.2 lbs.) of *pure* $NaOH$ to change 800 grammes of CO_2 into Na_2CO_3. This hydrate would cost about $1.28. Commercial $NaOH$ is seldom pure, however. Seven hundred grammes of oxygen per 24 hours corresponds to about 5.36 *gallons* per hour. In large cylinders oxygen sells for about 2 cents per gallon, in small cylinders at from 4 to 6 cents per gallon.

[4]G. N. Stewart, Manual of Physiology, 5th edition, p. 214.

oxide which I have used is, I suspect, within the limits of its relative proportion of the cost indicated. I have, however, wasted a good deal of oxygen and sodium hydrate in various experimental procedures. The cost should be less with ether or chloroform than with nitrous oxide. With respect to ethyl chloride, ethyl bromide or "somnoform" I have usually found from five to ten cubic centimetres sufficient for a fifteen pound dog. (From ten to twenty cubic centimetres would probably be sufficient for a man for the "dead space" of the machine requires as much vapor for a dog as for a man.) These drugs are best used when supplied in small glass ampouls of 3 c.c. or 5 c.c. capacity. A short rubber tube with a piece of cotton or gauze in the lower end is attached to the nozzle of the air-cock (28) and the drawn-out end of the ampoul is inserted like a cork (air-tight) into the upper end of the tube. The cock is then opened and the pump started. When all is ready the end of the glass ampoul is snapped off by bending the rubber tube and the drug quickly enters the air system. One must watch that the sudden entrance of a large volume of vapor does not over-distend the breathing bag. This can usually be checked by stopping the pump suddenly which tends to retard the passage of the vapor forward into the bag. For this reason small ampouls of very volatile bodies are better than large ones.

The duration of anæsthesia by this method is usually limited only by the convenience or desire of the operator. With nitrous oxide I have been easily able to keep dogs anæsthetized for periods of time extending up to a little more than *five and one-half hours* and the animals are in excellent condition at the close of the anæsthesia. The animal may often stand up and walk around the room within one and one-half or two minutes after it is removed from the nitrous oxide, but after a very long anæsthesia usually from five to nine minutes are required for complete recovery. With ethyl chloride one and one-half hours is the longest time that I have so far tried to keep an animal anæsthetized. (This is not a good anæsthetic for dogs.) With ethyl bromide I have kept dogs anæsthetized for periods up to a little more than an hour. With ether or chloroform the duration of the anæsthesia may be regulated practically entirely by the desire of the anæsthetist.

Summary

1. A new method for the production and maintenance of general analgesia or anæsthesia is described.

2. A description of the device required for the production of analgesia or anæsthesia by this method is given.

3. Great care has been exercised to confine the descriptions in this article strictly to results which have already been obtained by experiments on dogs. (But the conclusion is easily drawn that similar results may be obtained in man.)

SPECIFIC TREATMENT IN TYPHOID FEVER

By Frederick P. Gay, M.D., Berkeley, Calif.

THE history of the specific treatment of typhoid fever divides itself readily into two definite eras, the first beginning with the work of Fraenkel[1] in 1893 and extending approximately for 20 years to 1912, and the second from the latter date to the present time. In offering this critical summary of the past history, present status, and probable future of a specific therapy against this malady, we may, to a large extent, omit a detailed consideration of the facts of the first of these two eras that has been mentioned, since it has been fully reviewed repeatedly in the past by each successive observer of the methods concerned. A rather full discussion of this subject will be found in the articles by Callison[2] and by Krumbhaar and Richardson,[3] and particularly in the systematic treatises on Typhoid Immunization by Fornet[4] and Friedberger.[5]

As has been already stated, Fraenkel in 1893 reported the results he obtained in treating 57 cases of typhoid with cultures of *B. Typhosus* that had been heated to 60 degrees. The vaccines were administered hypodermatically and fairly good results were obtained. The specificity of the action of typhoid vaccine that was assumed by Fraenkel in those of his cases which did well, was subsequently open to doubt from observations of Rumpf[6] who claimed that he obtained equally good results by using cultures of *B. Pyocyancus*. The accuracy of his observations, however, was subsequently questioned by Kraus and Buswell[7] and Presser.[8] Petruschy[9] in 1902, used typhoid vaccines in combination with immune serum and in several cases found this treatment was followed by a fall in temperature during the subsequent three or four days. Pescarolo and Quadrone[10] later used living avirulent cultures in treatment.

By far the greater number of reports on the use of vaccines in the treatment of typhoid fever during this earlier period were made by English and American writers, and did not differ essentially in the results obtained or in the methods employed. Ordinarily heat-killed vaccines (56 degrees—60 degrees) were employed in variable dosage and at varying intervals during the course of the disease. Fornet[4] has summarized the results of 15 authors who report more or less favorably on the results obtained in over 300 cases. Callison[2] has extended this list to include some 747 cases. The consensus of opinion, with few exceptions, of the authors during this period, is that the use of the vaccines when given under the most favorable conditions of dosage and interval, shortens the course of the disease, lessens mortality, diminishes the percentage of relapses and complications, and may, in some instances, give rise to rapid defervescence and cure. We are, in these cases, at best dealing with relatively small differences in percentage in comparing the treated cases with those that have been used as controls. The instances of abortion of the disease, although exceptional in this series of cases, was mentioned as early as the work of Fraenkel who obtained it in two or three cases. A further consideration of this rapid amelioration, which apparently followed the use of vaccines, will be considered in more detail in connection with the more recent

methods of treatment. At best, no very striking results can be claimed for the use of the ordinary vaccines administered subcutaneously in the treatment of typhoid fever.

In addition to the use of the more usual types of vaccines, it may be mentioned that autogenous vaccines have been suggested by various writers, notably Thiroloix, Garsaux and Bardon;[11] Josue and Belloir;[12] Sacquepee and Chevrel[13] and Bourke, Evans, and Rowland.[14] In a similar way Ramond and Goubert[15] have suggested a process of autohemotherapy by subcutaneous injections of the patient's own blood drawn from the veins and injected directly into the adjacent connective tissue. By such means they claim a distinct benefit in 38 per cent of their cases. Bourke, Evans and Rowland have suggested using 60 to 300 millions of living typhoid bacilli derived from the blood of the patient who is treated.

Before passing to the more recent work in the use of vaccines, reference should be made to attempts at the treatment of typhoid fever by means of antiserum or antitoxins. The most favorable results that have been reported by this method are those of Chantemesse[16] who produced typhoid vaccines by growing the bacteria on extract of spleen and immunizing horses with this preparation and later with the living cultures. By means of serum obtained in this manner Chantemesse claims to have reduced the mortality in his wards from 17 to 4.3 per cent. Rodet and Lagriffoul[17] have reported the use of an antityphoid serum prepared by themselves, in 65 cases, which seems to shorten the course of the disease and in some cases to abort it if given early, that is before the tenth day. Ludke[18] immunized goats against toxins and living cultures of typhoid and claimed favorable results on patients given intravenous injections of this immune serum. Less favorable results have been reported in the use of antiserum prepared by Besredka, by Andriescu and Ciuca,[19] and by Ciuca, Combiescu and Balleanu.[20] Moderately good results have been reported by Gaupp[21] who used an antiserum prepared by Kraus in 16 cases. Kœnigsfeld[22] injected the serum of the individual patient in doses of 2 to 4 c.c. after the Widal had become well established, and found a distinct, though slow, improvement of the disease in 14 out of 18 cases. Ramond and Goubert[15] have reported good results in 38 per cent of cases by means of an autohemotherapy. Perhaps the best comment on the use of antiserum in typhoid fever is the short list of those who have described its effects at all, and the fact that many of those authors have subsequently reverted to the use of vaccines.

Interest in the specific treatment of typhoid fever has been rapidly developing during the last three years, and particularly during the last year and a half. Not only has the number of publications been larger than during the twenty preceding years of attempt at specific therapy, but the results obtained are far more striking and of a distinctly more convincing type. As in the previous years the best results have been obtained by the use of vaccines, but two important modifications in the vaccine treatment of typhoid have recently been introduced; namely the use of sensitized (Besredka) vaccines instead of ordinary vaccines; and second, the intravenous injections of the vaccines themselves. These two modifications, either employed separately or more particularly when combined, had led to a surprising increase in the percentage of aborted cases of the disease, the infrequent occurrence of which has already been noted as

having been observed from the time of Fraenkel. Not only does the very considerable per cent of cases that may be aborted by the more recent methods lead one to feel confident that methods have finally been determined, which, from the results obtained, are distinctly indicated as a rational treatment, but the results themselves give far greater confidence that they are due to the treatment and not to chance, spontaneous cures. It is of course recognized that rarely in cases of typhoid fever, during the height of the fever and perhaps even early in its course, the temperature may fall by crisis or lysis. When such results, however, are obtained in 30 to 50 per cent of the cases, and early in the disease, the element of spontaneous cure may be safely eliminated when the results follow directly after specific treatment.

Kraus and Mazza[23] and Kraus[24] reported in 1914, the favorable results that, in a number of cases, followed the intravenous injection of 50 to 100 millions of Vincent's typhoid vaccine (polyvalent and ether killed). Such injections are followed by a rise in temperature of 1 to 2 degrees, with a chill and then a rapid fall in temperature to normal or subnormal which may remain permanent. Thiroloix and Bardon[25] reported that they also obtained better results when typhoid vaccines are given intravenously and when they are autogenous. The fact that this action is not strictly specific has been evidenced by the work of Kraus[24] who found that he produced similar results in typhoid fever by the use of *B. coli* vaccine. Lüdke[26] claims to have actually cured certain cases by the use of deutero-albumose. Rhein[27] used the Halle vaccines diluted to a considerable extent and also administered intravenously. In a series of 33 cases he found that abortive cure took place within two days in 30 per cent, and in 48 per cent the fever was distinctly shortened.

But even better results have been obtained by the use of sensitized typhoid vaccines. These vaccines, which were originally suggested by Besredka in 1902, consist in either living or dead bacteria that have been treated, or sensitized, by means of an immune serum which is active against the organism in question, with subsequent removal of the excess of serum by washing. Such vaccines, particularly in the case of typhoid fever, have been shown, on the basis of the experimental work of numerous observers, to possess the following advantages over the ordinary, untreated vaccines. They give rise to transitory, passive immunity followed by active immunity that is as lasting as that secured by using untreated vaccines. They have the further advantage of producing distinctly less symptomatic disturbances than the ordinary vaccines. In their experiments on apes Metchnikoff and Besredka[28] found distinctly better protection against typhoid fever, which can be produced in these animals, by vaccinating with living, sensitized typhoid bacilli than by some of the other vaccines that have been devised, and used for the production of immunity in human beings. These sensitized vaccines have subsequently been extensively used for prophylactic immunization with success. In recent publications Gay and Claypole[29] have shown that either living or dead sensitized typhoid vaccines, but particularly the sediment of the alcohol-killed sensitized vaccines, protect rabbits against becoming typhoid carriers better than several other unsensitized preparations that were tried. For a further discussion of the use of these vaccines in prophylaxis, we refer the reader to this article.

Boinet,[30] in 1913, reported the use of Besredka's living, sensitized vaccines

in 15 cases of typhoid fever. When administered subcutaneously these vaccines were found to shorten the course of the disease distinctly and without any harmful effects. Ardin-Delteil, L. Negre and Maurice Raynaud[31] obtained similar results. The same authors further showed that although animals and patients treated by sensitized vaccines did not produce high agglutinins, the bacterial substances of their blood are distinctly increased, which results correspond exactly to those of Garbat and Meyer,[32] in experimental animals. Rouques[33] found that relatively large doses of Besredka's vaccine apparently led to distinct symptomatic improvement in a number of cases he observed. This was particularly true when the vaccine was used early in the disease.

Ichikawa[34] was the first to suggest the use of sensitized vaccines intravenously. He treated typhoid bacilli with the serum of patients who had recovered from the disease, injected this sensitized vaccine intravenously and obtained a considerable number of abortive cures of the disease by such means. He was able, moreover, to obtain almost equally good results in the treatment of paratyphoid fever with these same sensitized typhoid vaccines, indicating again, as did the work of Kraus, that the results obtained are not strictly specific. Garbat[35] who used a method essentially similar to that of Ichikawa, except that the vaccines were given subcutaneously, found favorable results in 17 cases, but only two abortive cures. His communication illustrates the superiority of the results attained by intravenous injection as introduced by the Japanese investigator. Paltauf[36] has reported similar results obtained by Biedl and by Eggerth, who compared the use of Besredka's living sensitized vaccines, intravenously, with Vincent's killed polyvalent, unsensitized vaccines likewise delivered directly into the veins. Far better results were obtained with the sensitized vaccines. Whereas Biedl reports only moderately good results, Eggarth in his letter to Paltauf, and also in a subsequent communication[37] succeeded in aborting the disease with a single injection in 31 out of 43 cases (72 per cent). Feistmantel[38] likewise found Besredka's vaccine to give better results on intravenous administration than the untreated vaccines of Kolle. He gives the treatment on four successive days in relatively small doses, and in 52 cases produced a rapid cure with critical and rapid lytic fall of temperature. These observers all agree that the method is harmless. The only dissenting report is from Sladek and Kotlowski[39] who, on the basis of four cases, in which distinctly good results were produced, emphasize the possible danger of collapse and heart failure.

Reference has already been made to the work of the author and Claypole[29] which led us, from experiments on rabbits, to believe that the best typhoid vaccine for prophylactic purposes consists in the sediment of alcohol-killed, sensitized bacteria from which the endotoxins have been removed. Good protective results with little symptomatic disturbance at the time of the injection, have been obtained with this vaccine in human beings. Certain of our experiments with a phenomena described as specific hyperleucocytosis[40] led us to suggest the intravenous injection of this sensitized vaccine in the treatment of typhoid fever. We found that the injection of typhoid bacilli in specifically immunized rabbits gave rise to an acute hyperleucocytic crisis in about 18 hours which frequently reached an extraordinary height (150,000 or more leucocytes to a cubic millimeter) and which was coincident with the sterilizing of the body from

the injected living bacteria. It seemed evident that this high leucocyte count was brought about by the increased attractiveness of the injected bacteria when they had been acted upon by the immune serum in the animal's body, for leucocytes, since it was found that a similar specific phenomena could be produced by injecting sensitized typhoid bacilli, that is bacilli treated with immune serum, intravenously in normal rabbits.

These results and the apparent relation of this increase in leucocytes to the recovery of the animal from the infection, led us to hope for further results in treating cases of typhoid fever intravenously with sensitized vaccines than with the unsensitized vaccines. Although this means of treatment was in mind before the publications on the intravenous injections of sensitized culture that have been mentioned, no opportunity was available for trying out this method until recently. Owing to the courtesy of a number of physicians in Oakland, Berkeley and San Francisco, we have recently been able to treat a few cases of typhoid fever and have obtained favorable results in harmony with those writers that have been mentioned, in a distinctive percentage of cases, and also certain indications which may lead to a further perfecting of the method. We have given intravenous injections of our sensitized vaccine sediment in 19 cases of typhoid fever, in which the diagnosis was fully confirmed by laboratory as well as clinical means. In 14 of these only was it possible to carry out the treatment exactly as intended, and these cases only are used as a basis of study. In this preliminary report we prefer to deal only with those cases in which an abortive cure was effected, following one, or in some instances, more injections of the vaccine. We have left out of consideration those cases in which just claim to shortening the duration of the disease or amelioration of symptoms could properly be made, owing to the impossibility of controlling such apparent improvements in a small group of cases. Of the 14 cases considered, 5 were cured abortively, or 35 per cent. Of these cases, two received a single intravenous injection; two received 2 injections and one received 3 injections before the temperature came to normal permanently. The average day on which the temperature reached a permanent normal in these cured cases, was the 19th. We find that adult patients readily tolerate the intravenous injection of a suspension containing about one-twenty-fifth milligram of sensitized vaccine sediment, which corresponds to 300 million of the living organisms. This dose has, in no instance, produced severe symptoms and may readily be increased on subsequent injections, when such prove necessary. The only alarming symptoms that have been noted were in connection with a patient who received by error an injection of 800 million bacteria and in this case there were slight hemorrhages from the mouth and distinct evidences of collapse which, however, were only temporary. The symptoms produced by the intravenous injections of vaccine in the cases mentioned, agree entirely with those that have been noted by other observers, notably by Ditthorn and Schultz;[41] Kraus and Mazza;[23] and Kraus.[24] In from 15 to 30 minutes following the injection the patients experience a distinct chill which may be decidedly unpleasant. The temperature rises from 1 to 2 degrees and we find that coincidentally there is a distinct fall in the number of polymorphonuclear-leucocytes, say from 6,000 or 7,000, to 3,000 or 4,000. In one or two hours the temperature begins to fall, the patient often perspires freely and experiences a very marked amelioration of general symp-

toms. At about 12 hours after the injection the temperature has reached normal or subnormal, and the leucocytes in most cases have increased, in some cases to as high as 20,000 to 40,000 per cubic millimeter. We have not as yet sufficient data to state whether the degree of hyperleucocytic crisis is of prognostic significance.

In our series of cases one relapse and no complications have occurred, so we are unable to state whether the treatment has affected them or not. Although the earlier writers on the use of typhoid vaccine seemed to think that subcutaneous doses on several occasions had a beneficial effect in diminishing the number of complications and relapses, later writers, Guinon and Malarte;[42] Ditthorn and Schultz;[41] Goldscheider and Aust;[43] and Csernel and Marton[44] find complications unaffected by vaccine particularly in those cases where if favorable results occur they are of the abrupt, abortive type. We have had two fatal cases, one of which died early in the disease, following several days of coma and delirium, and the other distinctly later, of no recognized cause, the autopsy being refused. Neither of these cases was apparently affected favorably or unfavorably by the treatment, with the exception that the temperature fell following nearly every dose that was given, and there was a temporary amelioration of symptoms.

We seem to have the best results by repeating the injections, when necessary three or four days apart. This allows for an abortive cure following the first injection, for although the temperature falls to normal the first day it may fluctuate for a day or two subsequently rising to 100 or 101 degrees and at the end of this time fall to normal and remain there permanently. In our experience if the second or third injection fails to produce more than temporary effect, little can be expected from further injections in the way of abortive cure. The procedure of other investigators may be mentioned in this connection simply as showing the variation in methods of dosage and intervals than have been employed. Kahn[45] advocates the use of 3 million to 5 million organisms given subcutaneously at intervals of three or four days. His favorable results, when present, are not, however, of the abortive type. Pensuti[46] gave 400 million gradually decreasing on successive days to 100 million subcutaneously and obtained a percentage of abortive cures. Kraus[24] gave 50 to 100 million of Vincent's vaccine, intravenously. Goldscheider and Aust[43] have used 250 to 750 million of unsensitized vaccine subcutaneously. These variations in dosage mean little beyond the limited experience of the author, and depend on the type of vaccine and the results desired. In our experience when an abortive cure is attempted enough vaccine must be given to produce a distinct reaction in the way of a chill with rise and fall of temperature. When treatment is directed toward symptomatic improvement, the dosage of course, as with the older types of typhoid vaccines, may be smaller.

It is of particular interest to us to note that there has been apparently some relation between the absence and occurrence, and indeed of degree of occurrence, of the Widal reaction and the results obtained. All of the cases that have been cured abortively by intravenous injections of vaccines have had a positive Widal, and in several instances a Widal that was distinctly high, for example 1-320 or 1-640. In several cases the exact titer of the agglutinin was not obtained, and in some cases may have been higher than the simple diag-

nosis of "positive" would indicate. In two at least of our failures the Widal has been persistently negative when treatment was attempted, and in none of them did the agglutinin titer exceed 1 to 80. This fact, if it prove to be consistent, would indicate that the successful abortion of the disease would depend on the strength of the antibodies that may have been produced in the patient's blood. In other words, if a resistance is already effectively established the additional impulse produced by injecting the vaccine is sufficient to tip the balance in favor of recovery. One might go further and assume that the hyperleucocytic crisis which we have shown occurs in animals and in human beings following the injection of sensitized typhoid vaccines, produces results only when there are sufficient antibodies present in the patient to affect the bacteria that are present in the circulation and cause them to be more readily phagocyted. It is interesting in this connection to note that Pensuti[46] found that those cases which were unaffected by his vaccine treatment gave a constantly negative Widal reaction. Koenigsfeld[22] obtained the best results from auto-serum therapy by using the blood of the patient when the Widal was high. In the cases reported by Sladek and Kotlowski,[39] the successful abortive cures were accompanied by unusually high Widals. The beneficial effects of high antibody content in the patient is further indicated by our observations as well as those of Ditthorn and Schultz,[41] who found that the most striking results are secured after the 10th day of the disease rather than before, although the older methods of amelioration of the symptoms and shortening of the disease by subcutaneous injections of vaccines state that the earlier the treatment was begun the better the results. Recent experience would seem to indicate that the course of typhoid fever is not markedly affected by the use of vaccines during the incubation period as is evidenced particularly by the cases reported by Elmer[47] and by Goldscheider and Aust.[43] These results are not of necessity in contradiction to the statement of Vincent,[48] who thought he had prevented the occurrence of typhoid in known cases of infection by the use of vaccines. In his cases no controls were possible.

To *summarize* the history of the specific treatment of typhoid fever: The first twenty years' experience since 1893 with the use of ordinary preparations of typhoid vaccines administered subcutaneously gave some encouragement for the method in the matter of symptomatic improvement, shortening of the duration of the disease, decrease of the mortality, lessening of relapses and complications, with a few abortive cures. The results attained were of doubtful value and inspired little confidence that the true "heroic," specific, treatment had been found. Modern investigations have introduced the intravenous administration of dead or living cultures and particularly of sensitized cultures of the typhoid bacillus. With such methods far more striking results have been realized. Abortive cures occur in a considerable percentage of cases, perhaps in as high as 30 to 40 per cent. If our working hypothesis is correct, these abortive cures are due to the presence of antibodies in a patient who is actively combating the disease and cure is effected by the action of these antibodies on the circulating bacteria combined with a specific hyperleucocytosis produced by the vaccine, particularly when it is specific and is sensitized. The remain-

ing cases might possibly be favorably affected by a combination treatment of sensitized vaccine and a suitable immune serum which would supply the lacking antibodies.

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LABORATORY AND CLINICAL EXAMINATIONS

By George Dock, M.D., St. Louis, Mo.

THE founding of a journal devoted to the laboratory side of medicine leads one's thoughts to some consideration of laboratory practice. A radical change has taken place in the minds of the profession as regards laboratory work. We have turned a point that often caused professional shipwreck. That point was the belief that laboratory methods were not only apart from, but antagonistic to the other methods of diagnosis. The belief was based upon a fundamental error—viz., that there must be short cuts to diagnosis, and that these were offered chiefly by laboratory methods. Now the urine, now a section of tissue, now a blood spread, lured the hope that by a glance one could tell what perhaps a long and careful study of anamnestic or physical findings had failed to reveal. In truth, there were reasons for the belief, for it often happened that the search was successful to a striking degree—too often, unfortunately for real progress, for with such a viewpoint the name of the disease, or of some disease, was the chief aim of diagnosis. To the superficial diagnostician, as to the layman in daily life, the name seems the great desideratum. Of course the old view will only slowly disappear, more slowly in some places than others, but it is certain that what was formerly a commonplace is now becoming more and more rare. As examples, even now one may occasionally discover myxedema in a patient sent specifically for a urine examination in a case long called Bright's disease, or a leukemia under similar circumstances, neither blood nor urine having been looked at in either case. But it is becoming rare to find a patient long treated for malaria when a physical examination and sputum examination would have disclosed tuberculosis months before, and it is refreshing to find the same improvement as regards septic endocarditis. Ignorance of the conditions of instrumental diagnosis long led to characteristic mistakes and recriminations. For histologic examinations, blood clots or granulation tissue were blindly scraped off from an ulcer or a cervix and much disgust was expressed because early diagnoses of malignancy were not made. For a sputum examination saliva or food remains were presented, notwithstanding careful directions for obtaining the proper material. Obviously, clinical examinations were no more thorough or accurate where such methods prevailed. After explaining, in a public lecture, the absolute necessity and also the value of inspection in suspected pulmonary tuberculosis, the patients brought in for a clinical demonstration were told they need not undress, and as each garment was reluctantly taken off, from overcoat down, at my repeated request, the "cases" were advised by my recent auditors that that was enough. It was no surprise to find in the first patient, one who was a great puzzle in the local medical circles, and whose sputum had often been almost sent to the state laboratory for examination, complete immobility of one side of the chest and other signs of advanced disease. The change of view is due partly to different opportunities for studying medicine, partly to a much larger body of medical knowledge. Patients as well as physicians have come

to realize that laboratory diagnosis is a part of diagnosis in general; that it is capable of giving information of value, often of cardinal importance; that like all other diagnostic methods it varies in value and in certainty in different cases and at different times; that its chief function is not to give names but to reveal details of many and various kinds. Such details are etiologic factors, anatomic or functional conditions of organs, or the biological or chemical constitution of certain secretions or excretions or fluids, all of which go to make up the real diagnosis of the patient's case. An interesting index of the change is found in the fact that some who have been very successful laboratory specialists are preparing themselves for some or other department of practice,—not because they care more for the latter, but because they see a narrowing field of practice for the laboratory. I have spoken of changes in methods of study. For a long time after laboratory methods were available,—the description of tube casts by Henle in 1844 makes a conspicuous epoch, not only physicians long in practice, but even recent graduates, were totally untrained in laboratory methods. Only those who devoted special time and who had special opportunities could do the work, and their aid had to be called upon even for the most ordinary matters, such as albumin or glucose tests, blood counts, etc. Now that practical teaching has been so widely adopted and hospitals and dispensaries give so many opportunities for clinical practice the present generation no longer needs the aid of specialists, but finds it better, for many reasons, to make its own laboratory tests. Moreover, physicians of the older generation, untrained in laboratory manipulations, could not work up newly discovered methods, in their irregular and uncertain leisure hours, even if they understood the new technical terms. Those who have been properly prepared in laboratory manipulations and principles can develop facility in new methods without difficulty, from journal articles or books, and cannot so readily lose touch with the constant advance of medicine.

The change in teaching and in opportunity for practice has exploded a fallacy that hampered many. I refer to the view that some people have no talent for laboratory work. Of course there are differences in natural manual dexterity, in sharpness of vision, in color sense and other particulars, but one who has worked with many undergraduates finds few indeed who cannot become facile in any branch of laboratory work.

Widespread acquaintance with the rudiments of diagnosis can easily be continued and enlarged by all beginning practitioners, none of whom should begin without a laboratory equipment and the determination to enlarge his fund of knowledge and experience, of observation and experiment. Besides the cultivation of special skill, other advantages will follow. The greatest gain will not be the economic one. Far greater in importance will be the earlier diagnosis in its prognostic and therapeutic bearings, and perhaps even more so, the growth of well-founded confidence on the part of the physician.

Laboratory tests, like all others, are often needed promptly. If one must wait for a report even for a few hours, vital time may be lost. So the trained physician will make most of his laboratory examinations, or at least have them made in his office, for much of the work can be made by trained assistants who need not be physicians. Most men will probably wish to see albumin tests, urine sediments, sections and blood smears, as they will prefer to see

eruptions, throats and eyegrounds, to percuss and auscult. But they need not count leucocytes, nor make ordinary titrations, any more than they take temperatures, because such details can safely be left to others and give the physician time for work that he can do better than others.

But the laboratory specialist will continue to have a field, and a more important and interesting field than ever before. Many serologic methods, now so necessary in practice, can be carried out on a large scale as well as on a smaller one. Many chemical investigations can be done while other manipulations are being carried out, and some laboratory workers will develop special skill that may be invoked at times just as do many ordinary clinical methods, and this skill will be kept up and increased by the larger material that comes to the specialist in any line. New tests will often be referred to such experts by physicians who have not time to work at all the methods proposed, although the young physician with spare time will often spend that time in just that kind of work, knowing that all such experiences have a training value comparable to other clinical work. It may even have a relatively greater value, unsuspected at first, as in the case of the X-ray or even the electro-cardiogram. The wide use of the former is obvious, the need of the latter not so well known. In the early days of the string galvanometer it was rather widely accepted that although useful, indeed indispensable for the detection of certain rare cardiac anomalies, its function would for a long time be limited to physiologic research. It soon became clear that although the field for research is still large and inviting, the instrument is capable of replacing all the older instruments used for making objective records of the heart's work, and surpasses them all in the light it throws on many problems of cardiac pathology. Special laboratory work need not be done in private institutions. Hospitals have in the past sadly neglected it, but they are rapidly making up for this and their laboratory staffs will naturally be called upon to do many of the special examinations.

With a general acceptance of the views set forth, a periodical devoted to laboratory methods must have a field as large as that of even the most general clinical journal. It must interest and be necessary to the general practitioner as well as to the special laboratory worker, must be a source of information alike to those who do the work and those who have others do it.

At such a time one who has long been working in the laboratory may be permitted certain comments on contemporary methods. Such common neglects illustrate the incomplete recognition of the use of all diagnostic methods. Let me illustrate this with two examples. At a certain period of the history of medicine it was believed that the finding of elastic tissue in sputum was a valuable aid in the diagnosis of pulmonary tuberculosis, at that time recognized chiefly in its later stages as consumption. After the discovery of the tubercle bacillus that work was abandoned, just as some people abandoned physical examination of the lungs after the discovery of X-rays, and sent their suspects to X-ray laboratories without so much as a glance at the thorax. But the finding of elastic tissue has a distinct and special value. Without regard to its rarity in processes other than tuberculosis, that tissue, usually easy to recognize, is readily found when present, and indicates with absolute certainty a breaking down of lung tissue. This isolated fact should be of a value comparable to that furnished by the thermometer or the blood counter, and should

therefore be sought by all who wish to have accurate knowledge of their patients. The other example is the detection of myoidema. This also was once heralded as a sign of consumption. It would be idle to consider it in that way now, but as a sign of a peculiar condition not yet understood, it deserves further attention in all cases in which it occurs, just as the more popular skin and serum reactions. One can often see the necessity of learning the relative importance of diagnostic methods and their practical application. This can best be done by critically noting one's results, but some fundamental principles may be emphasized. Examinations should be as complete as possible, but just as one cannot, for example, note the details of hair in all cases witnout the danger of overlooking something more important, so can similar things happen in laboratory practice. As one must observe the hair in cases of possible ductless gland, so in certain cases the rarer organic compounds in the urine must be worked out. But more than once I have known men to make quantitative tests of many rare urinary elements and fail to note a pyuria or bacilluria. Certain venerable errors should cease. An interesting book might be written about the mistakes in the microscopic examination of stools. There are some troublesome elements in many stools, but surely the noting of vegetable tissues such as spiral ducts or cereal hairs for parasites should not continue, now that all medical students have to study the elements of biology. Among the many errors in this respect that have fallen under my observation one of the most pathetic and remarkable was that of a middle aged physician whose life was made miserable for years by the diagnosis, repeated by many men in various parts of the country, of spiral ducts for hookworms.

Another common error in laboratory diagnosis is in expecting finality when the conditions do not warrant it. One still sees a diagnosis of typhoid rejected, and inferior treatment carried out because a Widal test is negative. This is all the more unfortunate because it has been recognized for a long time that the Widal reaction is not to be looked upon as an early sign of typhoid. Many other negative results are wrongly assumed to be final, such as the absence of tubercle bacilli on a single examination, the symptoms continuing. One of the great advantages of laboratory methods is that having certain data established, one can put the patient on a physiologic treatment and follow up the progress of the case with the necessary laboratory tests. This is especially true of some obscure blood disorders and is applicable to many cases with renal alterations, while in glycosuria it finds its most valuable if not its most brilliant field.

Another point often misunderstood is the place of the laboratory test in the course of the examination. Following many formal schemes for case taking, the laboratory work is usually done last, though if specimens are available there is no reason why they should not be examined at once. In many cases the further work is much simplified by making the laboratory examinations first. If positive, the rest of the examination can be developed on more accurate lines than otherwise; if negative, that information is utilized so far as conditions warrant, and the examination proceeds in the usual way.

Not saving of time, or of thought, is the primary object of any diagnostic method of value, but the more complete and accurate knowledge of the patient's condition. The fuller and more exact the diagnostic data, the more certain will be the treatment.

ON THE PROBABLE TOXIC EFFECTS OF PROLONGED ADMINISTRATION OF PARATHYROID GLAND

By Roger S. Morris, M.D., Cincinnati, Ohio.

THE effects of prolonged administration of powdered parathyroid gland are so imperfectly described that the following case seems worthy of note,—the more so, as it possibly sheds light on the clinical manifestations of hyperactivity of the parathyroid gland.

A middle-aged married woman was referred to me more than two years ago. For a number of years she had suffered with paralysis agitans.

There was nothing of importance in the family history or in the patient's past history.

The present illness had begun insidiously several years ago, as already stated. Various therapeutic measures had been tried without success. Some twenty months before the patient came under my care, fresh parathyroid gland of the ox was administered daily for several weeks. Then, about eighteen months before I saw her, this was discontinued, and she was given Armour's powdered parathyroid gland, grain I, in capsules thrice daily. Apparently, there was improvement in the patient's symptoms for some months.

After eleven or twelve months of parathyroid extract administration, the patient is said to have begun to fail. However, the powdered gland was continued uninterruptedly, until she came under my care. The history during this time, as I have been able to obtain it, is unsatisfactory, for the patient's recollection of recent events is dim, and for a part of the time her memory is a blank. From the nurses' bedside chart, the greater part of the data is obtained.

For at least three months, the patient's mental state had been abnormal. She was oriented in regard to place but had no idea of time. There was apparently great indifference to surroundings; she took little or no interest in what happened. She usually refused to answer questions, though there was no interference with speech or hearing. Her memory was poor. She often refused food or medicines; for a time it was necessary to conceal the medicines in the nourishment. When the patient did talk, speech was often incessant for an hour or more, and usually what she said was irrational. She was frequently irritable and cross. In the night, especially, she was apt to sing for an hour or so at a time. For many months she had a purposeless habit of knocking on the wall.

Auditory hallucinations were present. No visual hallucinations were noted.

Insomnia was one of the earliest symptoms to make its appearance, when the patient began to fail. It is impossible to give any definite statements previous to the time the special chart was begun. For three months the amount of sleep the patient had has been accurately recorded by the two nurses who were constantly with her. From their notes, the accompanying chart has been made. From this it is evident that the patient's sleep never amounted to as much as seven hours, except the first day charted. On this occasion the patient

slept only three hours during the night, but had five hours' broken sleep during the day. The longest period of uninterrupted sleep the patient had during the first two months charted was about two and a half hours. She was always very restless and wakeful.

Motor unrest was pronounced at times. The patient would toss about in the bed, pitching her body and throwing arms and legs. Because of this, it was necessary to have someone with her constantly, to prevent the patient's falling from her bed.

For three months or more, the patient urinated and defecated in bed. There was apparently no loss of sphincter control, as subsequent events seemed to show. Rather, the patient was quite indifferent to what happened. Her language and manner were at times coarse, quite at variance with the charming, sensitive, highly refined individual she proved to be.

Much of the time the patient had tachycardia, the pulse being between 100 and 106, weak and irregular, as recorded on her chart. The blood pressure was not measured until seventeen days after discontinuing parathyroid; then it was 120 m.m. Hg. systolic. Menstruation occurred regularly at the normal interval of time. There was rather marked anorexia.

At my first visit, I found the patient lying in bed in the dorsal position. She seemed quite unconscious of those about her, and from time to time made brief comments, which evidently related to auditory hallucinations.

The patient was well nourished. The color of the skin and mucous membranes was good. There was no enlargement of the lymphatic glands; the thyroid gland was not enlarged; there was no thrill or murmur over it. The pupils were equal and reacted actively to light and accommodation. The patient refused to co-operate in attempts to test the extra-ocular muscles. The tongue was moist and clean, the teeth in fair condition.

The lungs were clear on percussion and auscultation.

The heart apex was neither seen nor felt. By auscultation the sounds were loudest in about the normal position. Relative cardiac dullness was not increased. The sounds were rather weak but clear. The pulse was regular in force and rhythm, 24 to the quarter minute, rather small in volume, of fair tension. There was no thickening of the vessel walls.

The abdomen was about on a level with the ribs. Liver and spleen were not felt; by percussion neither was enlarged. There was apparently no tenderness on palpation, and there was no rigidity.

There was a small bed sore over the sacrum.

No tremor was noted in the extremities. The tonus of the muscles was distinctly increased.

The biceps and triceps tendon reflexes were present. The knee jerks were present and were not increased; the plantar reflexes were normal. There was neither patellar nor ankle clonus. The abdominal reflexes were present.

Sensation could not be tested satisfactorily.

During the course of the examination the patient defecated in bed. She seemed perfectly unconscious of the fact. It was soon evident, however, that the passage of urine and feces in the bed was not due to loss of sphincter control—for the patient asked for the commode at times and used it,—but rather

to her mental state. Urine was normal. The blood was also negative. A differential count was made; it was normal. The record was unfortunately lost.

Within two days after my first visit, parathyroid gland was discontinued, and the patient was given tincture of nux vomica before meals, veronal and cold sheet packs at night. The second night, after discontinuing parathyroid gland extract, the patient slept seven and a half hours with the aid of 7½ grains of veronal. This was the best night's sleep she had had since the bedside chart was begun three months previously. Within a week, involuntary defecation ceased entirely, and after two weeks, the patient no longer voided urine in bed. The tenth day after opotherapy was stopped, the patient slept two and a half hours during the day and seven and a half hours during the night without veronal, which was then discontinued. In the two years which have elapsed since then, she has slept well and has rarely required drugs. The bed sore healed promptly.

For about two months after parathyroid extract was stopped, the patient

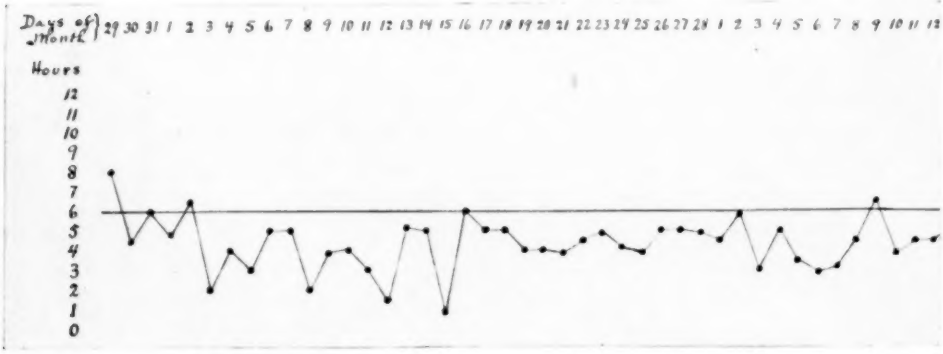


Chart showing the amount of sleep daily.

remained abnormal mentally, though she showed steady improvement. She was very willful and obstinate and insisted on having her demands granted. She often exhibited childish retaliation when not allowed to have her way.

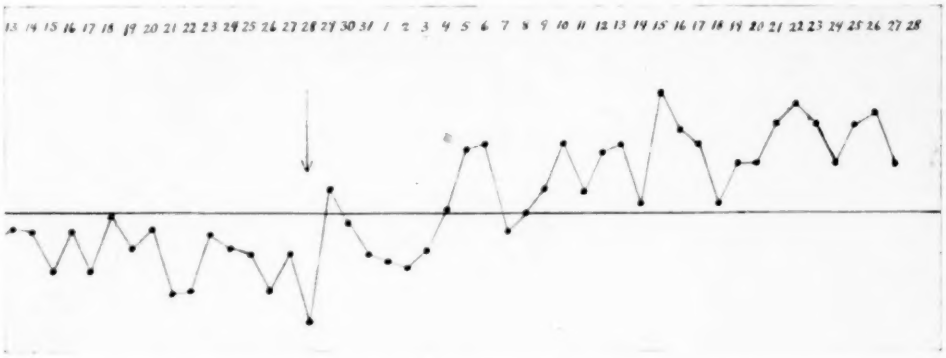
Seventeen days after parathyroid extract was withdrawn, the patient was wakened from sleep by a convulsion of short duration, which involved chiefly the flexors of the extremities, the nurse reported. It lasted only a few seconds. A more accurate description could not be obtained. The next morning when I saw the patient, physical examination showed nothing more than previously. Thinking that the convulsion might possibly have been due to the discontinuation of the parathyroid gland, Trousseau's and Chvostek's signs were tried; each was negative. Nevertheless, the patient was put on calcium lactate and was given one grain of Armour's parathyroid gland substance every third day. There has been no recurrence of the convulsion.

The mental condition of the patient finally became normal, nearly three months after parathyroid was stopped. She said she had no recollection of events for six months, including the first two months of her convalescence.

The tremor became more pronounced ten days after stopping parathyroid gland substance and has remained so.

The evidence points strongly to the view that the symptoms narrated above were due to the powdered parathyroid gland which the patient received for eighteen months. The promptness with which recovery began after the gland was withdrawn is suggestive. Furthermore, in the text-books which I have consulted on Parkinson's disease, I have been unable to find a description of symptoms similar to those my patient suffered from; it is certainly not a usual complication of the disease.

The dosage of parathyroid gland is very indefinite. I have been able to find practically nothing in the literature. It would seem, however, that my patient received liberal quantities, for she was given one grain of the powdered parathyroid gland (Armour's) three times a day. This is so prepared that one grain of the powdered gland is equivalent to six grains of the fresh gland. When one recalls that the total weight of the four fresh parathyroid glands, in man, is usually 0.14 gram, according to Thompson,[1] it would seem that the equivalent of 18 grains or 1.2 gm. of *fresh* ox parathyroid per diem would be an over-



The arrow indicates the day on which parathyroid administration was discontinued.

dose. Indeed, it seems surprising that unpleasant symptoms did not occur sooner after beginning the treatment.

A description of toxic effects from the administration of parathyroid gland, I have been unable to find in the literature. Berkeley[2] refers to it very briefly in discussing the treatment of paralysis agitans with parathyroid nucleo-proteid, prepared according to Beebe's method. He says, "I have had but one or two patients out of the hundred or more in my own care who really had an idiosyncrasy for ox-parathyroid. These could not take it in any form or dose without such disagreeable by-effects—'nervousness' and insomnia—that it was impracticable to continue the medication." Brief though it is, this would seem to have an important bearing on the case reported above, in which insomnia was so striking.

Salvioli and Carraro,[3] in an experimental study of the effect of watery extracts of ox-parathyroid gland on the circulation, reported a fall in blood pressure following intravenous injections, which was not due to local action on the vessel wall, nor was it from action on the vasomotor center. They concluded that parathyroid extract acts as a poison on the heart muscle, whose strength it lessens. This observation may possibly throw some light on my

case. During the height of the supposed toxic symptoms, in addition to the moderate tachycardia already noted, there are frequent entries on the bedside chart describing the pulse as "weak" or as "irregular." The pulse was small and weak, but I was unable to detect any irregularity, though it must be recalled that the patient received the extract less than two days after I first saw her.

As the symptoms from which the patient suffered were chiefly mental, it is impossible to reproduce the condition in experimental animals. Similar experiments in man are, of course, not to be considered. As a result, the interpretation of the case, as I have outlined it, must remain in doubt for the present, at least. It seems possible, however, that somewhat similar clinical syndromes may eventually be found to be due to overactivity of the parathyroid glands,—in other words, to hyperparathyroidism. Should such prove to be the case, it would lend support to the supposed toxic origin of the symptoms in my patient.

It is a very great pleasure to acknowledge with sincere thanks my indebtedness to Dr. W. S. Halsted of Baltimore for his generous assistance to me in searching the literature.

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PRECANCEROUS CONDITIONS OF THE SKIN

By Martin F. Engman, M.D., St. Louis, Mo.

HISTOLOGICAL investigation of all precancerous conditions points to primary or preliminary changes in the corium and its vessels before there is any obvious proliferation and downgrowth of the epithelium. These preliminary changes in the cutis seem to be brought about by various clinical factors which may be divided for study as follows: (1) Senility; (2) Actinism; (3) Chemical trauma; (4) Mechanical trauma; (5) Chronic inflammatory diseases.

1. *Senility.*—Little is known of the anatomical and chemical changes coincident in the senile skin. No standard has been established as to what should be considered senility of the skin. Both the microscopic and macroscopic appearance depend so much upon external and internal conditions that it is almost impossible to establish such a standard without numerous controls in its study. In fact, senility is such a broad term and includes so many conditions that are taken for granted, as being due to the natural wear and tear of life, that it is probable that many at present unknown remediable conditions are included in this process. Senile changes in the body may begin at any age, but they are particularly early in those whose mode of life subjects them to exposure to the elements and whose subsistence is obtained by hard toil.

The physical changes of senility are probably first observed in the exposed parts, particularly upon the face and hands. The progress of the change is somewhat different in the two locations. The first changes occur on the backs of the hands in the form of unnatural freckles, the earliest sign being the persistency of freckles upon the forearm and hand. In those in whom senility is beginning, the freckles persist from one season to another; they are larger than those usually seen in youth and are of a deeper color. Upon the backs of the hands only a few may persist and become organized, as it were,—that is, they become slightly raised above the surface of the skin in the form of flat papular lesions which may be smooth or be covered with horny or friable scales. In the beginning of senility, such scaly lesions generally undergo involution, but later they are more persistent and remain for a longer period of time. As years progress, they become still more permanent and may develop into wart-like excrescences, or remain as flat scaly lesions which extend peripherally to various dimensions; not infrequently they degenerate into carcinoma. Some of them become deeply pigmented[1] and are seen upon the hands as very dark or brownish scaly plaques or warty growths. Coincident with or preceding the pigmentation and the formation of the warty or scaly plaques, atrophy begins in the skin and its appendages. As the process develops a change in the pigmentation and character of the skin occurs over the whole surface of the back of the hands; the skin becomes yellow and wrinkled, and when taken between the fingers, seems to be almost as thin as tissue paper; the blood vessels showing through as if the skin was almost translucent. Cheattle,[2] quoted by Crocker,

[1]The Precancerous Melanoses of Dubreuilh.
[2]Cheattle: Allbutt's System of Medicine, vol. ix, p. 612.

refers to this condition as "biotripsis" or "life wear," and although he states the condition is due to exposure, yet it may be seen in aged individuals who have not been exposed to the elements.

Senile changes of the skin of the face make their appearance later than those upon the hands. They are introduced by some wrinkling and change of contour about the angles of the lower jaw, which progress upward over the face. An erythematous blush over the seborrheic areas sometimes occurs quite early, followed by pigmentary deposits, particularly over this region and near the hair line. The pigmentation occurs as dark or yellowish deposits; some of them seem to be buried deeply in the skin as black or yellow plaques. These dark, pigmentary lesions occur most frequently about the temporal regions and over the cheeks.

Independent of the pigmentary change, greasy, scaly plaques occur over the seborrheic areas of the face and chest, in the form of wart-like growths or horny projections, in which the scales may be friable, greasy and yellow, or of a dirty blackish color, and are easily removed with the curette. When the horny or friable scales are removed from these lesions a bleeding surface is exposed, covered at its edges with a soft necrotic material which is easily scooped out. Such lesions are called keratosis senilis, verruca senilis, or seborrheic warts, and are very frequently the site of malignancy. Following the pigmentary and keratotic changes, atrophic spots soon supervene. They occur most frequently about the sides of the cheeks and the lower lids, and are often the cause of ectropion. Telangiectases and nævus-like lesions soon appear, following atrophy, and even before the atrophic changes are marked, they may be scattered irregularly over the seborrheic areas of the face and chest. Therefore, in the more marked cases, senility seems to give the patient almost the appearance of one suffering from xeroderma pigmentosum.

Senile changes progress more slowly upon the covered portions of the skin, but frequently there are found upon the back and chest, senile warts in great numbers, which usually attain to a larger size than they do upon the exposed portions; many of them having the clinical appearance of nævi, and in many instances late appearing cell rests. In individuals whose occupation constantly exposes them to the strong sunlight and the action of the elements, senility begins earlier in the skin and is quite marked in all of its various clinical manifestations, and therefore in these individuals in whom such active changes are progressing carcinoma is more prevalent. Unna has given the name "sailor's skin" to those senile changes apparently induced by exposure to the elements, as he observed them most frequently in those whose life was spent upon the sea. Similar peculiar changes in the skin are seen in cab drivers, farmers, laborers, and others whose history shows exposure to outdoor influences.

Senile and pigmentary changes occur in all individuals coincident with old age, no matter whether they have been exposed to the elements or have led sedentary lives. In the latter, these manifestations occur much later in life than in those who have been exposed to the weather. It is well known that in all scaly conditions upon the senile skin, independent of the cause, there is a marked tendency to malignant infiltration by the epidermis.

The histological study of the senile skin is interesting, especially when one uses the tinctorial dyes of Unna, which demonstrate conclusively early degenera-

tions in both the connective and the elastic tissue elements. The beginning of senility of the skin can be demonstrated by a change from the normal reaction of these tissues to these dyes.[3] There is, likewise, a progressive atrophy of all the elements of the skin and its appendages, which accounts for the falling of the hair, the dryness of the skin's surface, and its curious wrinkled, yellowish appearance. Nutritional disturbances occur early in the process, no doubt due to degenerative changes in the cutaneous vessels, and it is very probable that if histologically examinations were properly controlled, the vessel change could be demonstrated to be the forerunner of the nutritional and degenerative processes in the skin. If one of the small keratotic lesions be neucleated and examined microscopically it would be found to consist of an increase of perakeratotic cells which force themselves downward into the cutis, dipping with finger-like downgrowths between the papillæ of the corium. The lesions are not inflammatory, but there is a certain amount of round cell infiltration about the invading epithelium. The upper epithelial portion of some of them is quite horny, giving them the clinical appearance of warts, while in others, the outer cells are parakeratotic, retaining their nucleus and sponginess, therefore forming a more friable and scaly surface. In the latter type, the scales are usually more or less greasy, containing more oil, giving to the surface a greasy, seborrheic element, which is no doubt due to the atypical, physiologic cycle of the parakeratotic cells. Such lesions may start from a small point and increase their dimensions by peripheral extension into rather large, scaly plaques or wart-like excrescences. It is very suggestive to watch the development of these lesions from the smaller types to the larger, so much so, that one feels secure in assuming that this is the earliest stage of malignancy; and it does not seem to be a great step, morphologically, between the invading peculiarly changed epithelium of a seborrheic wart and the malignant process that has seemingly sprung from it; but biologically, it is a chasm, as we have still to determine what is the element or elements which cause these invading cells to infiltrate.

Only in comparatively few of the invading warty lesions does malignancy occur, and in this respect we are in the same position as Cohnheim, when he looked about for a stimulus to explain the malignant step that occurs in his "embryonic rests." In fact, Pollitzer and Unna believe seborrheic warts to be only "seborrheically degenerated, soft nævi." Downgrowth of epithelium does not mean a beginning of epitheliomata, as one would seem to gather from morphologic studies by various writers upon this subject. The various anatomical changes produced by the invasion of such proliferating epithelial cells, as one finds in all such growths, are accidental in many of their phases, as such a mass of cells may invade the mouths of follicles and push aside certain elements of the cutis, causing certain reactionary inflammatory changes. Histological evidence does not disclose the vital step that has occurred biologically in these growing cells; the agent that has caused them to infiltrate and destroy the surrounding tissue. In many of the non-malignant downgrowths of the epidermis, one may find nests of cells which attempt to physiologically functionate and form whorls, but even this does not signify that they are malignant. And the same peculiar clumping of the chromatin, changes in the cell-walls, atypical mi-

[3]Himmel: Arch. f. Derm. u. Syph., 1903, p. 47.
[4]Kreibech (Arch. f. Derm. u. Syph., 1903, p. 325) found fatty degeneration of elastic fibres similar to that found in arteriosclerosis.

toses and the various other morphological microscopic features which are said to be significant of precancerous change are also found, even more frequently, in other pathological conditions of the skin which rarely if ever becomes cancerous.

2. *Actinism.*—Light is supposed to cause the change in the skin seen in xeroderma pigmentosum, and we know that the X-ray causes certain changes in the skin similar to those seen in that disease. We have also seen that the senile skin is similar in its clinical manifestations to xeroderma pigmentosum, therefore, it is safe to assume that the ultra-violet rays of the solar spectrum have much to do with the production of the senile skin in certain individuals. It may be possible that such rays activate some element in the skin which through its influence causes these degenerative and atrophic changes. But if this be due to chemical change induced by light, it is only in certain individuals that it occurs. Xeroderma pigmentosum is a pre-senile condition and may occur at any age; but unfortunately we do not know the active underlying factors, merely the physical changes which mark the progress of the process by the production of pigmentation, which is, no doubt, an effort of nature to protect the more delicate elements of the skin from the light rays. The dark skin of people of the tropics suggests this, and therefore when we see pigmentation following such exposure to light, we naturally assume that the pigmentation is formed in an effort to protect. Unna believes that such superabundance of pigment acts pathologically upon the skin, which may be true and explanatory of some of the changes induced in this class of diseases. The skin of one who is suffering from the sequellæ of repeated attacks of X-ray dermatitis is similar in its clinical symptoms to xeroderma pigmentosum and to the skin of the very aged in whom pigmentation, keratosis, and atrophy are quite marked. Hyde and various other writers wish to attribute to the actinic rays of the solar spectrum a marked pathogenicity in the production of carcinomata of the skin. They assume that it is only in a certain hypersensitive proportion of individuals in whom this action occurs: "Pigmentation, telangiectasis, atrophy, keratosis, and cancerosis of the skin occur in adults much more frequently than in childhood, reaction to the play of actinic rays of light upon the surface being generally determined after the middle periods of life have been reached." (Hyde.)

3. *Chemical Trauma.*—In certain individuals, whose occupation exposes them to the irritating influence of certain chemicals, there occur inflammatory conditions of the skin which are frequently followed by malignant change. Chief among these is the so-called "chimney sweep cancer" which occurs most frequently upon the scrotum, induced by certain elements in the soot, which constantly irritate the skin. Schamberg has suggested that this may be due to an actinic principle contained in the soot. The so-called "kangri" carcinoma occurs in the natives of Kashmir who wear a small earthenware stove, called a "kangri," attached to a belt beneath their clothing: the heat or friction from this stove irritates the skin and causes a chronic dermatitis, which in many instances ends in cancer. Analine workers and those who work in paraffin, tar, pitch-blend, and various chemicals which cause irritation of the skin, are subject to chronic dermatitis and wart-like growths, which frequently develop into carcinoma. Arsenic when taken over long periods or accidentally absorbed

into the system over long periods produces a hyperkeratosis and pigmentation of the palms and soles, which not infrequently develops into malignant infiltration.

4. *Mechanical Trauma.*—Mechanical trauma also may produce changes in the skin at the point of continuous irritation sufficient to induce malignant infiltration of the epidermis. We see this on the lip as the result of constant irritation by pipe stems and cigars, and in the mouth from the irritation of the hot smoke striking continually upon the same point; also in the betel nut chewers in Africa, particularly in the women, who rest the nut against the side of the cheek. A similar condition is caused by the tobacco plug in tobacco chewers. Various other sources of trauma, such as ill-fitting dental plates, especially in certain occupations in which constant irritation causes chronic dermatitis, frequently determine the site of malignant change, as pointed out by Wolbach in cattle, in which traction is made over the horn by a rope, causing at the point of constant irritation an inflammatory area which is followed by carcinoma.

5. *Chronic Inflammatory Diseases.*—In fact, all of the precancerous conditions present in the beginning, chronic inflammatory changes in the cutis, but what we wish to call attention to under this heading is the carcinomatous change which not infrequently occurs in the chronic ulcerations of syphilis and tuberculosis, in old patches of psoriasis, lupus erythematosis, lupus vulgaris, chronic ulcers of the leg, in Darier's disease (Wende), in old irritated, hypertrophic scars, burns, and in various other chronic inflammatory diseases of the skin. In fact, one must realize that in every one past middle life or even earlier, malignant change may occur in patches of skin that have been subjected to prolonged irritation from inflammatory processes, no matter what may have been the source or cause of the inflammation. Leucoplakia of the tongue or mucous membranes of the mouth, inflamed tonsils, various keratoses of the tongue and mucous membranes of the mouth, or chronically inflamed teeth, at points of irritation from badly fitting dental plates, are frequently sites of malignant change. Therefore, in such chronically inflamed patches one must be on the lookout for pearly epithelial borders, for dark greenish crusts, for the heaping up of epithelial cells on the surface, for increased infiltration, for beginning ulcerations in patches that were formerly not ulcerated, together with some infiltration and pearly condition of the border, as these symptoms are indicative of malignant infiltration.

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The study of precancerous conditions just given conforms suggestively to the theory of Ribbert. All of them give microscopic and clinical evidences of long continued disturbance of the cutis (the connective tissue), the supporting framework of the skin, accompanied by various forms of abnormal cornification, parakeratosis and less frequently hyperkeratosis with peculiar changes in the nuclear body, chromatin and cell wall, so called degenerative processes.

With Wolbach, we cannot help leaning in these instances to the theory of von Hansemann, who believes that "the tumor cell is one that has suffered modification, characterized by a loss of the power of differentiation and the acquisition of increased powers of growth." In all of the instances of carcinomatous change occurring in inflammatory conditions, the irritation or in-

flammation has preceded the malignant change by a number of years. In other words, it seems necessary before malignant change occurs in these instances, to have a prolonged disturbance in the life-cycle of the cells of the part or site, where malignancy occurs. Here is where Ribbert's theory is somewhat applicable: a disturbance of the physiological functions of the epithelium induced by the prolonged change in their cycle of growth preceded or followed by snuffing off of a portion of the invading interpapillary pegs by the connective tissue. At this time the cancer may be considered "to be a parasitic individual engrafted on a normal individual," and that they are produced by the conjugation of cells in a "way anomalous to the conjugation of sexual cells which produce a normal individual." (Nichols.)[5] It is interesting to note here that carcinoma has been produced in a rat by prolonged X-ray exposure, which is possibly the only experimentally produced carcinoma on record. Wolbach in the study of X-ray cancer maintains that the acquisition of malignant powers is only completed during years of active proliferation, accompanied by progressive impairment of nutrition, as all of the carcinomata occurring in X-ray dermatitis supervene only after the dermatitis or inflammatory process has existed for years.

It is curious to note that in Wolbach's investigations, possibly the earliest changes seem to occur in and about the cutaneous vessels, which is the case in all precancerous conditions. There is in all of them early evidence of nutritional change, which probably disturbs the physiological function and the life cycle, of first, the connective tissue cells, followed much later by those of the epidermis—a tissue composed of cells of a higher type, whose functions are physiologically much more highly differentiated and whose biological characteristics render them more susceptible to all forms of irritation. They are therefore more easily sensitized to chemical and mechanical influences, as is demonstrated by the various peculiar epithelial reactions to external and internal stimuli seen in many non-malignant and malignant diseases of the skin. The biochemistry of all cells is greatly influenced by environmental conditions; therefore, the epithelium of the exposed portions of the skin and mouth are constantly subjected to these influences, which may explain the great frequency of cancer in exposed locations.

Constant interference in the normal metabolism and physiological functions of a cell will ultimately produce a cell physiologically and sexually atypical, which seems to be characteristic of the cancer cell when compared to the normal kindred cell of its kind. This is what probably occurs in all the precancerous processes, and has given to them the descriptive title of "Precancerous Keratoses."

Precancerous Keratoses.[6]—Under this term we have classed all of the above mentioned clinical conditions which seem to be followed in rare instances by certain distinct and definite morphological changes in the epithelial cells.

The precancerous keratoses occur so frequently after or are coincident with

[5]For theory of Farmer, Moore and Walker and an excellent work on "Tissue and Its Relation to Cancer," see Nichols (Jour. Med. Research, Jan., 1905).

[6]It is interesting here to note that according to the researches of Kreibech (Arch. fuer Derm. und Syph., vol. cxvll, No. 3), the melanoblast of Ehrman or chromatophore of Ribbert, the cells responsible for the melanotic pigment of the skin, are derived from the epithelial cells which have altered their morphological and physiological characters on the impulse of some stimuli. He believes that any epithelial cell may become a melanoblast and that it is identical with the nævus cell and the cell of the melanoma and possibly Paget's disease.

these conditions that they must be, at present at least, accepted as etiological factors, yet their exact causative relationship or influence in this respect is not known. However, we have the so-called precancerous changes occurring in the epidermis and producing distinct objective clinical entities without any apparent local contributing etiological factors. The principal member of this group is the clinical condition known in literature as Paget's disease.

Paget's Disease (malignant papillary dermatitis).—There are several types of this peculiar disease which shade gradually into one another. Sir James Paget was the first to describe the condition. As his cases occurred about the nipple region, a similar process in any other portion of the body caused some confusion in the proper understanding of the process. Since Sir James Paget's original description, many instances of the disease have been reported as occurring in various other parts of the body: the lip, vulva, penis, umbilicus, buttocks, chest and back. In my experience the midsternal, shoulders and back are equally as frequent locations as the breasts.

Clinically, the disease may be divided into a mammary type and an extra-mammary type. The clinical appearance and course differ somewhat in the two locations; also the histological features to a certain degree.

Mammary Type of Paget's Disease.—It is extremely rare, is usually unilateral, occurs most frequently in middle life and begins as a dermatitis-like eruption either on the nipple or the areola and slowly spreads over both parts. The earliest symptom is probably an itching or burning with reddening and distinct thickening of the tissues, accompanied by branny scaling. The process extends slowly, the surface becomes denuded of the horny epithelium, and is of a bright or dusky red color; crusts later replace the scales, and the whole surface takes on a disc-like infiltration with a sharply defined or raised border. The infiltration is distinct and card-like. The denuded portion may be covered with crusts or an oozing, sticky, homogeneous débris. The disease may remain in this stage for a long time, even years, before distinct clinical carcinoma of the breast develops. This is heralded by retraction of the nipple and the obvious formation of neoplasms in the breast itself, or the involved area becomes granular in appearance, ulcerated, greatly thickened and raised, with erosion of the nipple and deep excavated points of ulceration. The disease may extend far beyond the areola. Again, it may begin as a scurfiness and itching at the opening of the milk-ducts with a similar condition scattered over the areola at isolated points. This process extends very slowly until the whole region is involved. Usually a scirrhus form of breast cancer supervenes.

Extra-Mammary Type of Paget's Disease.—This type differs somewhat in its clinical and histological features from the former, but to all intent and purpose it is the same process modified through location. It is very difficult to conform the various reports upon this subject into a succinct description, as writers portray so varied a picture. The most suggestive and valuable article is that of Bowen, who points out the connecting links between the precancerous keratoses.

Paget's disease may be mistaken for a patch of chronic seborrheic dermatitis in extra-mammary locations, but it is a question if such a dermatitis can precede the entity known as Paget's disease. From our knowledge of Paget's disease, this is not probable. No one that I know of has watched the process

in these instances from their incipiency; therefore, when it is first observed by the physician, it has a characteristic appearance. It is always seen as a sharply circumscribed patch (in rare instances patches), situated anywhere on the body, with well-defined borders. The patch has a characteristic dusky pinkish tint, is slightly scaly and atrophic-looking—the whole picture showing a chronic progressiveness. The tendency is to progress peripherally, sometimes more in one direction than in another, giving the patch various shapes. One portion may cicatrize while another extends, or cicatrization may occur in the center. In very large patches where this has occurred, relapse in the cicatrized portion may be seen in the form of a superficial ulceration, a crust or crusts, or small nodules, an attempt at tumor formation. The process is very slow, chronic and superficial as a rule, and does not cause deep or large tumors unless a vital lymphatic region is invaded, like that of the vulva, penis, scalp or breast. On account of the location of the extra-mammary type, there is not the tendency to excoriation of the horny epidermis and oozing as seen in the mammary form. Crusts may form here and there over the surface, yet it is not the rule. A patch is frequently encountered which has an atrophic glistening sunken appearance with slightly raised borders and has almost the appearance of a healed lesion, not unlike that of a very chronic lupus erythematosis.

Extra-mammary Paget's disease is not as infrequent as one would be led to believe from the literature and the comparatively few reported cases. It is probably frequently unrecognized or is diagnosed as something else.

The process is slow and chronic, sometimes undergoes involution, and is very rebellious to treatment. One case of mine, which almost encircled the chest, involved and wiped away the right breast, lasted for 40 years, the patient dying from senility at the age of ninety-three. All portions of the process showed the typical histological appearances of Paget's disease. The breast was surgically amputated twenty years before her death and showed a slow scirrhus process. The left breast was involved years after, but was not removed.

The pathological process in all types is essentially a precancerous one, meaning by this term, one in which the epithelial calls show those well-known morphological changes which are frequently followed by and are often seen in carcinoma. Most authors believe that Paget's disease is from the very first a carcinomatous process, but we have long associated carcinoma only with tumor formation and typical malignancy. We must therefore broaden our view of carcinoma and malignancy and include those clinical conditions which show the type of cell so often seen in malignancy, together with clinical symptoms similar in their ensemblé to those produced by certain types of basal-cell cancer.[7] Then Paget's disease is carcinoma of a peculiar type, capable of producing under certain conditions and in certain localities carcinoma of various accepted varieties. Where the lymphatic arrangement and other conditions are propitious, Paget's disease produces typical, well-known types of carcinoma. For instance, I have seen two cases of a peculiar chronic seborrheic-like dermatitis of the lower lip, with oozing, crusting and some card-like infiltration in old men, which were followed in five and ten years respectively by carcinoma of the glands of the sub-maxillary region. Both cases were absolutely rebellious to

[7]Hartzells' (Jour. Cut. Dis., 1910, p. 388) remarks upon this subject are pertinent . . . "these changes we must regard as carcinomatous, just as we regarded as carcinomatous the overgrowth of the epithelial cells themselves."

all forms of treatment, X-ray included. These cases were undoubtedly Paget's disease of the lower lip.[8]

On account of the peculiar cell degenerations and inclusions found in this disease, Wickham and Darier thought it a disease *sui generis* and due to coccidia. This view has, however, been abandoned and the process is now looked upon as a peculiar type of carcinoma. The old idea that it has the appearance of "eczema" should also be dropped from literature.

Darier cites the following features as portraying its carcinomatous nature:

(1) Slow development during its earlier stages.

(2) Minor degree of malignancy.

(3) Involvement of lymphatic glands only occurring towards the latter part of the process.

The microscopic picture of Paget's disease is characteristic and unique on account of the peculiar "degenerative" (?) processes found in the epithelial cells and the reaction in the derma.

There is an edema of the epidermis which forces the cells apart and causes a swelling of the prickle-layer with distension of the nuclear spaces. The epithelium is increased in depth and pushes itself here and there into the derma. Mitoses are seen in the prickle-layer. The epidermis or horny layer is usually soon lost. The prickles disappear and the cells of the epidermis partake more of the nature and shape of those of the basal-layer as it increases in depth. Cornification goes on in a modified form, and together with the edema and possibly other factors produces throughout the section numerous atypical cells (probably a form of dyskeratosis) which were thought by Darier, Wickham and others to be protozoa. The nature of these cells is now known, and is more or less characteristic of several so-called precancerous conditions. Within a double contoured cell-wall there are peculiar faintly stained granular bodies with the appearance of a limiting membrane; the nuclear chromatin is clumped and the nuclear body peculiar.

The papillary body of the derma is flattened out and studded by plasma-cells, lymphoid-cells and frequently polymorphonuclear leucocytes and mast-cells. These surround the invading epidermis. The vessels are dilated and surrounded by new cells, especially plasma-cells. The process in the derma is of a granulomatous nature with a tendency to organization which causes retraction of the nipple and some of the induration. As the peculiar epithelial cells invade they also infiltrate and spread along the lactiferous ducts and initiate the scirrhous type of cancer, which is really the final stage of the disease.

The danger of the process lies in the infiltrating power of these cells which is so marked in certain regions, particularly the breast, that Jacobæus and others believe them to be gland-cells which have wandered into the epidermis from below, and that the local clinical condition is a result of the previous deep-lying carcinomatous process. Facts do not confirm this view. The extra-mammary type is not so edematous, the lymphatic channels not so widely dilated and subject to invasion; the horny layer is often thickened and parakeratotic and intact. The whole process in the derma is more chronic, not so severe or granulomatous in nature; however, the cells of the epidermis present essentially the same peculiar changes as in the mammary form, except possibly in degree.

[8]Histological material could not be obtained in either case.

STAINING SECTIONS OF LIVING TISSUE, UNFIXED*

By Louis B. Wilson, M.D., Rochester, Minn.

THE fixation of tissues by rapid killing and hardening before further preparing them for the microscope is now universally conceded as a necessary process in the study of many cell structures. It produces variations in the degree of refraction and degree of imbibition of cells and of portions of cells, thus making possible their optical differentiation. It also prevents post-mortem changes in cells, preserving their structures so that they may be studied at leisure. By coagulating fluids and by rendering insoluble certain tissue elements, fixation prevents their removal during subsequent manipulations. By the intelligent choice of proper fixatives and other reagents, we may kill, harden and prepare for the microscope almost any tissue without greatly altering the relative size or shape of its cell elements. The changes in refractive indices and in color reactions, while artificial, are not necessarily misleading though our concepts of the normal relations of cells are no doubt often greatly exaggerated.

While conceding the necessity for fixation in almost all instances for fine cell study, histologists are well aware of the desirability of studying living cells with the least possible manipulation. But living cells are indistinctly marked off from each other, and their complex internal structures have almost exactly similar refractive indices and little or no color variations. Thus, the microscopic examination of untreated living tissues, in other than ultra violet light, quickly runs counter to certain fixed principles of physical optics. Our problem then is the production of variations of color and refraction with the least violence to the cell and without coagulating its protoplasm.

That cells may be stained in the living animal has been abundantly shown by Ehrlich,[1] S. Mayer,[2] Apathy,[3] Bethe[4] and others. More recently the physiochemical processes by which living cells are stained have been studied by many observers, among them, Kiyono,[5] Michaelis,[6] and Evans and Schulemann.[7] The latter observers have shown that the chemical constitution of benzidine dyes is of no influence on the capacity of the dyes to act as vital stains except as it affects the physical state of the solutions of the dyes. Such dyes are taken into certain living cells by the same forces concerned in the reception of large particles (bacteria, carbon, etc.) into cells, forces based upon alterations in surface tension. The diffusibility of the stain determines only its capacity to reach the cells in a living organism. Its inclusion by these cells is not dependent upon a characteristic of the stain itself, but upon the vital functions of the cells.

Thus, by what has long been known as "phagocytic action," living cells take up certain dyes, but the process is a slow one and the ultra-microscopic particles of "colloid" solutions of the dyes are apt to be so grouped in the cells as to form definite microscopic masses, which may be mistaken for cell structures. This method of true vital staining has great possibilities, and its application is yet in its infancy. Its greatest interest, however, apparently lies in its biologic aspects, that is as an indicator of the differentiation of the func-

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tions of the various cells in the living body. The morphologist, and especially the pathologist making microscopic examinations of operative material and working in as speedy a manner as possible, will find more use for methods based on the principle of staining living cells whose surface tensions are already altered permitting rapid imbibition of dyes.

Many living cells which will not take up certain stains may be made to imbibe them by even so slight an alteration of surface tension as may be produced by shaking the cover glass on the preparation. Tissue freshly removed from the living body is still alive and remains so even after it has been quickly frozen, but the surface tension of the cells of the tissue has apparently been materially altered by the cutting off of the blood supply and by the freezing process. This alteration of the surface tension of the cells permits the rapid imbibition of certain stains, while at the same time the size and shape of the cells may have been altered in only a very slight degree, if at all, by the anæmia and freezing. Theoretically it should be possible thus to find just such a stage in cells, which are dying but yet not dead, that would permit of their differential staining while all their structures were fairly normal in size and shape. Any such method must of course fail both in the temporary preservation of the soluble elements of the tissue and in the permanent preservation of any of the tissue unless there is subsequent "fixation" (that is, coagulation of the proteins). Yet, such a method may give not only quickly obtainable pictures of the normal size, shape and arrangement of the cells, but also important details of the normal internal structure of cells, supplementing, and in some instances correcting, our concepts obtained from the study of fixed tissues.

Ten years ago in seeking some means of rapidly staining pathologic specimens as they came from the operating room that a diagnosis might be given while the patient was still on the table, to guide the surgeon in his further operative procedure, I worked out, from the basis of Bethe's methylene blue intravitum staining, a method which has since proved very satisfactory. It has been published twice before[8] but it may not be amiss to reproduce it here for the sake of those not familiar with it.

Details of Method of Staining

1. Freeze bits of fresh tissue, not more than 2x10x10 mm., in dextrin solution and cut sections 5 to 15 microns thick.
2. Remove the sections from the knife with the tip of the finger and allow them to thaw thereon.
3. Unroll the sections with a camel's hair brush or glass lifter in 1 per cent sodium chloride solution.
4. Stain 10 to 20 seconds in Unna's polychrome methylene blue.
5. Wash out momentarily in fresh 1 per cent sodium chloride solution.
6. Mount in Bruns' glucose medium.

The tissue must be fresh, that is, the cells must be still alive, and hence present no cytolytic changes. Almost all tissues which we examine have been removed from the body not more than five minutes, and usually not more than two minutes before they are frozen. However, we have gotten fair preparations in some instances from tissues that have been from one to two hours out

of the body. If kept in the ice chest under proper conditions, they may be stained after a still longer period. *Most failures are due to the fact that the cells are dead before the tissues are frozen.*

The dextrin solution is prepared by stirring dry dextrin into boiling water until the mixture is about the consistency of commercial maple syrup. Five-tenths per cent of phenol may be added in warm weather.

The ether freezing microtome is an unsatisfactory makeshift. Now, that tanks of carbon dioxide may be procured in every town which has a soda fountain, there is no longer any excuse for the use of the ether instrument. The microtome should be a well-made machine capable of cutting to five microns, though sections of many tissues cannot be handled quite so thin. In our experience, the best instrument for the purpose is the Spencer Automatic, though good results may also be obtained with the Sartorius, the Leitz and the new Bausch & Lomb instruments with mechanical knife carriers. A freezing microtome which is in constant service in a laboratory in connection with a surgical clinic receives hard usage and its parts therefore must be strong and well made. The valve for controlling the gas is apt to become quickly worn and leaky. This valve is more convenient if placed at the microtome and not at the tank. It should have a long flat T-shaped handle for ease of operation. Whatever style of microtome is used, the metal plate on which the tissue is frozen should be insulated in some manner from the metal parts of the remainder of the apparatus. This prevents the heat being transferred between the two, makes less gas necessary and keeps the tissue frozen longer.

The carbon dioxid tank should be suspended on metal hooks or brackets underneath the table on which the microtome is placed. Thus, the small amount of dirty water which is present in many tanks will not find its way into, and clog the valve of the freezing chamber, as it is apt to do when the gas tank is placed in a vertical position above the work table.

In freezing, the gas should not be turned on in a large stream and allowed to flow until the tissue is frozen. Much gas can be saved and much more satisfactory preparations made if it is turned on in intermittent spurts, giving time for the tissue to freeze more slowly, and thus more evenly throughout. It should not be frozen more solidly than is necessary for cutting. When this occurs, however, the upper layer may be thawed slightly by placing the finger on the tissue.

The sections should be cut by rapidly repeated strokes, not permitting the surface of the tissue to thaw after each cut. A half dozen or more should be cut, and the first ones rejected, insuring sections of even and uniform thickness.

In trimming out blocks of tissue for freezing, the pieces of tissue should be not more than 2 mm. in thickness, and the transverse diameter should be as small as is possible and still include the desired field of examination. The smaller the block down to 2 mm., the better the sections, and the more easily they may be handled. In general the blocks should be so trimmed that the sections when cut will be rectangular or rounded, rather than triangular in outline. Unless the block is more than 1 cm. in transverse diameter, the long edge should be so placed on the freezing plate that the knife edge will strike it

parallel. Where blocks are more than 1 cm. in transverse diameter, a shorter edge may be placed so as to first come in contact with the knife. When very minute bits of tissue are to be frozen, it is best to partially freeze a small amount of dextrin solution first, and then place the tissue on top of it, thus keeping it 1 mm. or more away from the metal freezing plate and avoiding contact of the knife therewith.

The knife edge must be as sharp as it is possible to make it. The blade should be very rigid, preferably wedge-shaped, and not hollow-ground. We have attempted to use safety razor blades in special holders, but have found them to vibrate altogether too much. Several blades, not less than four, should be provided for each microtome, since the edges are dulled very quickly with the best of tissues, and routine blocks are apt to contain unsuspected calcified areas. Reserve cylinders of carbon dioxid should also be kept in some nearby cool place, so that they may be changed rapidly if necessary.

When sections are removed from the knife with the tip of the finger and allowed to thaw thereon, a process which may be hastened by breathing on them, air bubbles are less apt to form than if they are removed with a brush and placed immediately in salt solution. As the sections go into the salt solution, they are usually more or less rolled up, and must be straightened out by gentle manipulation by moving them up and down either with a small camel's hair brush or with a bent glass lifter with a dull point. This is best done in a clear glass dish over a black background, permitting the unstained sections to be readily seen.

When the sections have been straightened out, they should be caught under the middle with a small bent glass rod lifter and transferred to the stain. If, in the stain, a direct up-and-down motion is made with the lifter, the section will remain thereon, the folded portions merely "flapping" in the stain. Occasionally a section will be lost off the lifter. If the receptacle holding the stain is large, much time may be lost and the section injured in finding it. This may be obviated to a considerable extent by using a very small receptacle, of not more than 10 cubic cm. capacity, with a rounded bottom. Small individual glass salt cellars and the small porcelain teacups from a set of doll's dishes are quite convenient. The bent portion of the glass lifter should be less than 1¼ cm. long and the end should be rounded in the flame.

We have never yet gotten an unsatisfactory lot of Unna's polychrome methylene blue direct from Grübler, while at the same time we have gotten one or more unsatisfactory specimens from every other dealer from whom we have purchased, even when the stain was said to have been made by Grübler and re-bottled by the selling firm. Now, that the German supply is temporarily cut off, we are making our own. The secret of success seems to be in taking a large quantity of Unna's alkaline methylene blue (methylene blue 1, carbonate of potassium 1, water 100), and allowing it to ripen for from six months to a year with the largest surface possible exposed to the air in a flask stoppered only with cotton. When the stain is properly ripened, it contains a considerable portion of methylene red, and should give sharply differentiated dark blue, purple and pinkish red color-contrasts with fresh tissue. The stain even in 5 or 10 c.c. amounts, may be used over and over again, but should be discarded when it shows a precipitate or when it no longer gives sharp color-contrasts.

The sodium chloride solution, which is used for washing out the gross excess of stain should be contained in a white porcelain dish, or if in a clear glass receptacle, this should be over a white surface. In this manner, the evenness of staining and the general appearance of the sections may be more readily seen.

Bruns' glucose medium is prepared as follows:

Distilled water 140 c.c.
Camphorated spirit 10 c.c.
Glucose 40 g.
Glycerine 10 c.c.

Mix the hot water, glucose and glycerine thoroughly, add the spirit, shake and filter to remove the excess of camphor which is precipitated on mixing. The solution should be kept in relatively small stoppered bottles. In warm weather a crystal of thymol may be added to prevent the growth of moulds. The solution is cheap, and should be thrown away as soon as it becomes colored with dye.

Sections are most conveniently spread out and transferred to the slide if the solution is contained in a long narrow porcelain dish about 1 inch deep by 1¼x4 inches. These may be obtained in the market as white porcelain match trays.

The section should be moved about in the glucose medium for a few seconds, not only to straighten it out but also to obtain better differentiation. The end of the glass slide is then slipped under it, the edge of the section held to the slide by the lifter, and the whole preparation raised out of the solution. The excess of glucose medium is wiped off from underneath the slide and around the section, the cover dropped on, and the preparation is ready for the microscope.

All the steps of the process may be carried out in one minute from the time the tissue is placed on the freezing plate of the microtome until the slide is placed on the stage of the microscope. Various tissue elements should be thoroughly contrasted in pink, red, purple and dark blue. Mitotic figures, when present, are beautifully shown. Many bacteria are stained.

The method, as given above, has been used for diagnostic purposes and for the study of fresh tissues in the laboratories of the Mayo Clinic for more than ten years. During that period it has been frequently modified by members of the laboratory staff. All such modifications, however, have been abandoned and the original method returned to. Probably the most useful modification is one which we used several years ago, and which has subsequently been independently developed and published by Pierce.[9] This consists in the substitution of distilled water for the sodium chloride solution, and of carbol-thionin for the polychrome methylene blue stain. The carbol-thionin stain may be more quickly prepared than the polychrome methylene blue, and is perhaps more stable. Bacteria are stained by it a little more sharply than by polychrome methylene blue. However, sections must not be left over long in the stain which contains 2½ per cent phenol.

Sections stained by the polychrome methylene blue method remain in excellent shape for two or three hours after the tissue has been removed from the body and may be in fairly good condition, if kept cool, for a day or two.

No satisfactory method has as yet been devised whereby desirable sections can be fixed and preserved after staining in this manner. Success in this direction probably lies along the lines indicated in Bethe's original method for the fixation of tissues vitally stained by injections of methylene blue.

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INTESTINAL STASIS AND INTESTINAL INTOXICATIONS: A CRITICAL REVIEW

By Paul G. Woolley, M.D., Cincinnati, Ohio.

ONE of the most widely discussed questions of the present day is that which concerns itself with intestinal intoxications arising during intestinal stasis. Its period of importance was inaugurated by Bouchard, who gave us that unfortunate term so widely used and so little understood,—especially in this connection,—*auto-intoxication*. Its greatest modern interpreter has been Lane, who has given into the hands of the many undiscerning a series of surgical procedures, awful at their best, but terrifying in the practices of the many who do not discriminate. It is a question on which much is written and of which little is exactly known.

The present vivid vogue of this question as a matter for discussion is more the direct result of the work and writings of Sir Arbuthnot Lane, for he has been able to make it more profitable than Metchnikoff, with all his erudition and experiment. Acting upon the assumption that a very large proportion of the ills from which men suffer are the direct result of absorption of toxic materials from the intestine, he has taught his methods, so that now surgeons (some surgeons) are everywhere seeking to remedy almost any condition by removing ceca, colons, and sigmoids, or all three, or by making unnatural intestinal anastomoses. When one considers the terrifying series of ailments which Lane lays at the door of stasis in the intestinal tract, one is, perhaps, thankful that there is so little evidence of the inheritance of acquired characteristics, or wonders why man was ever allowed a large intestine.

The term intestinal toxæmia, or intoxications of intestinal origin, refers to various symptom complexes which are associated with gastro-intestinal abnormalities of secretion, digestion, and motility. How great such a catalogue may be, one may discern by perusing the following list:[1]

1. Loss of fat.
2. Wasting of both voluntary and involuntary muscles.
3. Alterations in the texture and color of the skin with pigmentation and offensive perspiration.
4. Subnormal temperature, especially affecting the extremities. There is no abrupt line of separation between this condition and Raynaud's disease, of which it would appear to be a stage.
5. Mental conditions of apathy, stupidity, or misery, which may become exaggerated to a state of melancholia, or even apparent imbecility, with suicidal tendencies. There may be neuralgic symptoms, neuritis, frontal headache, loss of control over temper. These nervous states, due to stasis, are a much more frequent cause of serious crime than is generally imagined.
6. Rheumatic aches and pains in muscles, joints, and skin.
7. Atrophy of the thyroid.
8. Either increased or lowered blood pressure.
9. Degenerative changes in the breasts, especially in the upper and outer zone of the left breast, predisposing to cancer.
10. Prolapse of abdominal organs, partly because of loss of fat, partly because of wasted muscle fibres; increased mobility of the kidneys, and prolapse and bends of the uterus.
11. Breathlessness on exertion, at times of asthmatic type, due in some cases to a distension of the stomach and intestines.
12. Degeneration of the heart muscle with dilatation of the left heart and aorta and arteriosclerotic changes (atheromatous) in the systemic arteries.
13. Renal changes which are roughly grouped under the term "Bright's disease."
14. Early loss of hair color with falling out, more common in those with dark hair than with red hair.
15. Affections of the pancreas with chronic induration, inflammation, and finally cancer. Pancreatic diabetes.
16. Infection of the biliary system, cholecystitis, cholelithiasis, cancer, together with many acute and chronic diseases of the liver.
17. Degenerative changes of the eye.

All of these are results of absorption of toxic materials from the intestinal tract! All are primarily due to abnormalities of motility!

Watson[41] is more conservative than Lane. He divides his cases, whose histories are given, into three main groups; one in which the symptoms are mainly those of neurasthenia; one in which the symptoms are those of rheumatoid arthritis; and one which shows, mainly, dyspeptic symptoms.

Leaving to one side the problems which would arise in discussing motility, which is rarely a primary condition, and abnormalities of secretion, let us look at the possibilities connected with absorption from the intestine. They may be grouped as follows:

A. *There is the possibility that during digestion of food materials by the normal secretions of the gastro-intestinal tract, toxic substances are formed and that these substances may enter the blood stream and produce serious disorders.* As a matter of fact, we know that many of the products of protein digestion are toxic.[28] The peptones have well-known poisonous properties when they are injected into the blood stream. Even the unsplit proteins, such as egg albumens, are toxic under certain conditions. Vaughan[3] believes that the toxicity of proteins resides in the intertior of the molecule and that when this portion (its most chemically active part) is set free in the body, it acts as a poison because of its intensely active chemical nature. In the gastro-intestinal tract, if it is set free, it is immediately broken up by the ferments and so becomes harmless. The interior of the body is not constructed for such rapid or complete splitting, and so in the interval which would elapse between its liberation and its destruction, it damages the body and that damage may be shown by such symptoms as malaise, fever, or by such symptom complexes as anaphylaxis. Longcope[4] by injecting egg albumen into animals has been able to produce morphological changes in the organs, notably in the kidneys, which correspond to the milder degrees or stages of interstitial nephritis. Woolley, DeMar and Clark,[5, 5a] on the other hand, were unable to produce any observable symptoms or lesions by injecting egg albumen, casein or albumose into animals. Longcope's method was to activate his animals to egg albumen and then to produce mild attacks of anaphylaxis by subsequent injections of the same substance. Woolley and his co-workers treated their animals by giving them daily intraperitoneal injections of albumen, casein and Witte's peptone over a period of 40 days. It is possible that had they used Longcope's method they might have produced similar effects. The value of their work lies in the indication of the difficulty that is met in the passage of these substances into the tissues of the animals. Longcope's results indicate what may happen after the substances have entered. Wells,[35] some years ago, reported that by subcutaneous administration of Witte's peptone he was able to produce hepatic fibrosis. He, like Longcope, was placing the protein directly in the tissues. Wells now, however, doubts his results.*

It is a long known fact that it is with the greatest difficulty that any of the products of digestion enter the blood or reach the tissues in an intact state, under normal conditions. Somewhere in the progress from the lumen of the gut to the blood, they are so changed as to be non-toxic. There is also another side. Soluble substances of a toxic nature entering the blood tend to produce diffuse lesions rather than focal ones, and diffuse symptoms, rather than focal ones. One would expect, therefore, that soluble poisons such as the peptones and other split-products would produce generalized symptoms and lesions, and that focal lesions and symptoms might be due to localization of bacteria which enter subsequently. Evidence of this has been offered by Opie[6] who, with chloroform alone, was not able to produce the focal lesions he observed by injecting chloroform and colon bacilli.

*Contrary to many workers, Gibson (Philippine Journ. Sc., 1914, [8, B.] 475) who worked with very carefully purified proteins, which he injected with careful aseptic precautions into guinea-pigs (subcutaneously) says, "It would seem then, that the primary cleavage products of pepsin—hydrochloric digestion, when prepared without drastic treatment, from purified and well-characterized proteins, never have more than a slight pyrogenic effect when injected subcutaneously into rabbits and guinea-pigs. Any temperature rise, if present, is insufficiently pronounced to permit a direct inciting role to be ascribed to such proteoses in the production of the severe naturally occurring fevers." (cf. Jour. A. M. A., 1914 [62] 1835.)

It may be recalled in this connection that Ascoli, Oppenheim and others have shown that proteins fed to animals in large amounts may be demonstrated subsequently in the circulating blood and in the urine, though as Zinsser[7] says, this happens only under abnormal circumstances. Rosenau and Anderson also have shown that guinea-pigs may be sensitized by feeding horse meat or horse serum, and McClintock and King were not able to confirm it[7] which may only go to prove that McClintock and King did not encounter the abnormal conditions which made the results of Rosenau and Anderson possible.

The whole general trend of opinion regarding the absorption of protein split-products in a toxic state from the intestinal tract seems to be that while it is possible, it is unusual.

B. *There is the second possibility that bacteria resident in the intestinal tract act upon the food stuffs and produce toxic substances, which are absorbed and act as intoxicants.* Some of these substances belong in the great group of ptomaines, such as cadaverin, neurin, cholin and putrescin; some belong to the aromatic series, as, for instance, indol, skatol, and tyrosin. Para-oxyphenylethylamin is a recently studied substance; aldehydes have been under suspicion, and betaimidazolylethylamin (histamin) is challenged.[18]

As in the case of the protein split-products, there can be no doubt that these substances produce grave consequences when they are injected into the organism. There can be no doubt that they are continually entering the tissues through the walls of the intestine. But with exceedingly few exceptions they are so changed in passing the intestinal walls into the tissues, that they are rendered, so far as is known, innocuous. Hervieux[29] says that indoxyl is a normal constituent of the blood. Herter was among the first to use these substances in experimental work and his book[8] has become a classic. He showed that such substances as indol might be toxic, but neither he nor any subsequent writer has brought proof that they ever reach the interior of the body in amounts sufficient to be poisonous. There are two possibilities which would favor the toxic action of these products. One is that because of lesions of the intestinal tract so much is absorbed as to overtax the protective chemical action of the tissues and fluids of the body; and the other is that for some reason the protective combining power of tissues and organs is abnormally low. Concerning either possibility nothing is known. It is known, however, that the healthy body is able to take care of tremendously larger amounts of these toxic substances than are produced, as was shown by Woolley and Newburgh.[9 10] Iwao,[26] however, has been able to produce severe blood changes with minute doses of oxyphenylethylamin, but Charleton[27] produced similar effects with *B. coli* injected into rabbits. Under any apparent possibility, however, the absorption would not be the primary trouble, but some other factor which made abnormal absorption possible, and treatment should aim at correction of the primary condition rather than of the secondary.

Metchnikoff[11] is a valiant supporter of the bacterial toxic cause of many disorders, notably of old age, but he has never shown but one side, except by inference, in his writings. He has shown that by the use of certain organisms, notably *B. bulgaricus* and Glycobacter peptolyticus, the flora of the intestine may be changed, just as other writers[12 13] have shown that by diet similar changes may be effected. But he has produced nothing except incomplete cir-

cumstantial evidence that the general symptoms associated with an abnormal intestinal flora are due to the toxins or the protein split-products of the members of the flora. The presence of indican or phenol combinations in the urine in abnormal quantities is no sign that indol or phenol are acting as poisons in the organism, it is merely a sign that the contents of the large intestine are not in a healthy condition. Even if it be true, that, as Kendall (p. 136) says, "one is forced to the conclusion that the intestinal tract is a wonderfully perfect incubator and culture medium combined; in this intestinal incubator there is such a range of reaction and diversity of food stuffs that the most varied types of bacteria capable of growing at body temperature can conceivably find a place where the environment is particularly adapted for their development. It must be evident that the direction which the flora takes will not be without influence upon the host," there still are no solid grounds for saying that the absorption of split-products are the causes of symptoms—though they may be.

Distaso[25] has reported observations which show that so far as the anærobes of putrefaction are concerned, these organisms play no role in the putrefaction of feces within the body, and also that they perhaps play no role in pathologic conditions.

C. *There is the third possibility that the presence of bacteria themselves, which have entered the blood stream from the intestine, are the source of trouble.*

In support of this it may be said that the bacteria are constantly entering the body from the intestinal tract, and that under certain conditions, the number is increased. These organisms may produce either or both of two effects; they may act as irritants to the cells of the body (more particularly, perhaps, the endothelial cells), or they may, in being devoured by the cells of the tissues, liberate a toxic material which is either an irritant or a true poison. As an adjunct to this conception, it might be added that the soluble toxins of intestinal bacteria may be absorbed and act as poisons to the cells of the organism. In regard to this, one might say that except in very unusual conditions this does not happen, because, perhaps the toxins are modified in passing the intestinal wall exactly as other proteins are.

Adami[14] is the great sponsor of the infectious theory of the origin of fibrosis and other collateral effects. He believes that under certain conditions the usual minimal number of bacteria in the circulating blood is increased and that these produce organic changes. He speaks of the process as sub-infection. Ford[15] and others have studied the bacterial flora of healthy organs. Bierotte and Machida,[16] for instance, in discussing the bacterial content of the organs of healthy animals at a slaughter-house, found 10 varieties of germs in 59.2 per cent of 54 organs taken from 11 animals. An unpublished observation of Dr. Wade Oliver,[42] working in the Pathologic Institute of the Cincinnati General Hospital, is that the blood taken from the veins of patients, who are brought to the hospital in a state of fatigue, such, for instance, as following a debauch, is apt to show large numbers of organisms, especially ones belonging to the group of hemolytic streptococci. Dr. Oliver believes that the source of these is in the pyorrheic gingivitides from which most of these individuals suffer, or from other foci of chronic infection. Nevertheless, as the physical condition of the patients improves the blood becomes sterile. This observation bears up-

on the intestinal problem merely in indicating the comparative ease with which bacteria enter the body as compared with the difficulty with which non-living proteins enter. All of the recent work on "focal infections"[17] [17a] tends in the same direction, i. e., to indicate that the bacteria which are harbored in the body are able under certain conditions of general health to enter the blood stream and to be transported to the various tissues and organs of the body, where they produce focal lesions, and as has been said, it is focal lesions which produce focalizing symptoms.

It seems then that from the standpoint of the literature, the doctrine of infection is the more rational one. Perhaps it were better to say that in the production of symptoms during intestinal stasis the action of bacteria is the immediate cause, but that with this action, after a time, toxic materials may be absorbed through lesions in the intestinal wall produced by the intestinal contents. Accompanying stasis there are certain macroscopic changes in the mucosa which are readily recognized. One of these is a mild inflammatory condition, the others vary from more pronounced inflammatory lesions to ulcerations—such, for instance, as the "Dehnungsgeschwüre." An intestinal wall which is the seat of such inflammations is more permeable to bacteria than a normal one. Under such conditions bacteria and toxic materials pass into the circulation, during which process the latter become, as a rule, fixed, while the bacteria, protected by virtue of their being living, pass on until somewhere or other they become fixed and die, and their poisons are set free.

There seems to be good reason for the belief that many of the suspicious kinks and folds are not essentially harmful, for they are normal, or merely anomalies, and that most of them are of infectious origin[19]—the result of peritonitides. But of this more will be said later.

D. The fourth possibility is one suggested by Eppinger and Gutman and is one that has gained little credence, perhaps, because the problem has not been understood. These writers look upon many—perhaps all(?)—of the substances which pass the intestinal walls as homones, which reaching the tissues produce effects in the same manner as do the active components of the internal secretions,—i. e., by causing them to carry on more actively or less actively, as the case may be, their several functions. They point to the fact that B—Imidazolylethylamin (histamin) produces typical stimulant effects upon the autonomic nervous system, and that para-oxyphenylethylamin (tyramin) a split-product of tyrosin, resembles adrenalin in chemical and functional respects. So they would conceive of the intestines playing a role somewhat similar to that of the ductless glands.

E. A final possibility is that one or more of the previously discussed possibilities occur together.

We were negligent were we to leave the impression that with the five possibilities given above we had exhausted the possibilities in accounting for the symptomatology of so-called intestinal stasis. What we have tried to do has been to make clear the possibilities *from the intestinal side*. We believe that many of the symptom complexes credited to the intestinal conditions have primarily little or nothing to do with the intestinal tract, but that they are the result of infections elsewhere in the body. Lane, for instance, believes that pyorrhœa and oral sepsis are very common in intestinal stasis, as a secondary

occurrence. We believe with Watson[41] that they are primary. We believe, from the writings of Billings,[17a] Rosenow[17] and others, that when intestinal stasis occurs in conjunction with oral sepsis, it is merely a coincidence and not essential, and that the intestinal condition may become really a serious complication if the stasis is not corrected. Before such a complication occurs the essential place to apply treatment is the mouth. After it has occurred, both mouth and intestinal treatment are essential. In a like manner we believe that the primary difficulty in the rheumatoid arthritis group of cases, for instance, is probably to be sought elsewhere than in the intestine, and though we state this as a belief, yet we feel that there is abundant support of such a belief in the publications of Rosenow and others.[44] Cases are cited by Watson and others which definitely support such a belief. Even cases belonging in the neurasthenic group of Watson present evidence of the application of the laboratory results of the studies on focal infections in this group. The fact that Woolley[45] in a case referred to him by Dr. C. A. L. Reed, was able to obtain a pure strain of *B. lactis acrogenes* from a duodenal mesenteric lymph gland, does not mean necessarily that the epilepsy from which the patient suffered was due to that organism nor that the cause of the disorder lay in the intestinal tract—though that may be the truth of the thing. In such cases there is no method advanced for deciding whether the difficulty lies in an abnormal central nervous system which spontaneously reacts with explosions to normal stimuli or which reacts to abnormal (or normal) materials absorbed from the intestine or from some focus of infection in the intestine, or in some other organ. It may or may not be a rather hazardous attempt at prophecy when one describes the morphology and biochemical characters of the unknown microbic cause of a disease like epilepsy.[46]

Associated with these problems of etiology are those of therapeusis. These we may divide into two main categories,—medical and surgical. Within recent years the intestinal surgical treatment has come to the fore, reached its acme and seems now to be declining, the reason for this being that there appears to be a growing opinion that the therapeutic results have not lived up to their promises. It is the opinion of some, perhaps many, physicians, that the Lane operations for intestinal stasis belong in the same class with unnecessary ovariotomies, nephropexies, and appendicectomies.[18]

The intestinal surgical procedures include enterocolostomy, or enterosigmoidostomy, colectomy and cecectomy, and plastic operations devised for the removal of bands or kinks, chiefly in the course of the large intestine. The short-circuiting operations allow part of the intestinal contents to go more directly and rapidly to the outside world. It is a sort of flushing operation. Its main disadvantage lies in the fact that the isolation of a part of the intestine results in a condition in which the contents move more slowly and in which the feared fermentations and decompositions go on more vigorously than before the operation. The radical operations have the same effect upon the current in the intestine, but the vicious circle is removed. The cosmetic operation tends in the same general direction except that it tends to ease rather than speed. It straightens the crooked path without shortening it and eliminates the short turns. It is perhaps unnecessary to add here that if something wrong is going on in the bowel which shouldn't go on under normal circumstances,

it will not of necessity be right to remove the bowel. This, at first sight, would appear to resemble what might be done in case something were wrong with the drains of a house. One wouldn't necessarily remove the drain of the house, especially when he might improve or even cure the condition by running some chloride of lime through it. The difficulty with the plastic operations seems to lie in the danger of more adhesions, which are in turn inhabited and perhaps caused largely by bacteria. If, as Archibald[19] found, there are bacteria in the adhesions formed after simple operations in which there is no stasis, what would we expect in cases in which stasis is present? It is interesting to note that the only objection brought by Lane against complete colectomy is the development of post-operative adhesions.

What may happen, as the result of any or all of these operations, is that the feces spend a shorter time in the body and that therefore there is less opportunity for putrefaction, fermentation, dilatation and absorption, or that the bacterial flora is changed, or that both of these things happen.

The medical men, some of them at least, say[18] that they can obtain as good, or better results in the long run, with less hazard. They say that by using the methods of Metchnikoff they can change the flora; by diet alone[20 12 47] they can modify the flora; by laxatives they can hurry Nature and make her remove the garbage; by antiseptics[30] they can kill the parasites; and by mere copious water drinking[31] they can limit indol production and reduce putrefaction. And, they say, that while using these methods they do not need to worry about the septic tank of the short-circuit operations, the multiplied adhesions of the plastic, nor the mortality, or the adhesions following annihilation of the colon. Also they say that cecal or ileal kinks appear in 18 per cent of all persons[18] and that so many persons do not suffer from "intestinal intoxications." Again, they say that all who are constipated are not ill. Finally some may think as Einhorn believes, and quotes Dunin as suggesting it, that perhaps certain symptoms are not so much the results of constipation as they are causes of it. That there are colons which deserve destruction there can be no doubt, but it is suggested to try everything else first, and if there be no value in diet, exercise, massage, or physic,—use the knife. Eastman[37] says "it is probable that time will demonstrate the fatuousness of either short-circuiting or resection operations in cases of stasis not presenting demonstrable obstructing factors," and Lynch and Draper[38] feel that "surgery is able to offer *in selected cases* a therapy which often effects a true cure." Dr. Berghausen's work in the Pathologic Institute of the Cincinnati Hospital tends to support treatment (used by Watson and others) by vaccines in some cases of stasis. If this is justified, then there has been added another reason for belief in infection rather than in intoxication.

An editorial writer of the Journal of the American Medical Association[21] quotes Hale White, as follows: "When these cases are reported we are always assured that all medical means had been adopted without benefit, but we are never told what the medical means were. * * * * A suspicion comes to one's mind sometimes that perhaps some surgeons do not know all the means the physician has at his command for the treatment of delayed action of the bowels." This seems not to be unfair in many instances. Case[43] sums the situation up by saying that surgery should not be seriously considered as a cure for ileal stasis

until a most thorogoing trial has been made of the various dietetic and mechanical measures at our command.

But again, in discussing therapeusis we have confined our remarks to the intestinal aspect of the question. Washing out the intestinal tract will not cure pyorrhœa alveolaris though it will undoubtedly assist in cure. It will not prevent absorption from a root abscess, or from an area of decomposition under a crown or a bridge. It will not hinder the growth of staphylococci or streptococci in a chronic appendix abscess, or in the partially closed crypts of a tonsil; nor will it drive out the bacteria from the regional lymph glands in a case of arthritis deformans. For such focal conditions the treatment will vary—dentist, physician and surgeon, and perhaps even the bacteriologist, alone or together, may be needed, depending upon the seat of the primary infection.

Summary

By way of summary we may say:

1. That absorption of poisonous materials from a healthy bowel has not been shown to produce symptoms of disease.

2. That absorption of bacteria and other substances from an unhealthy bowel may produce serious symptoms.

3. A surgical operation for intestinal stasis is not justifiable except as a last resort.

4. There is no definite information in the literature to show that surgical procedures, made for intestinal stasis, have been more successful than medical (including hygienic) ones.

5. Many cases in which symptoms are attributed to intestinal stasis are suffering from focal infections entirely outside the intestinal tract. Such infections are illustrated by pyorrhœa alveolaris, chronic tonsillar infection, and chronic infections of the antra and sinuses of the head.

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LABORATORY METHODS

TEST for Albumin in Urine.—Heat and nitric acid, simply and combined, with the contact test, remain the reliable means for the recognition of albumin in the urine. All other tests are objectionable in some respect, and the findings, with them, are subject to misinterpretation. The tests for albumin should be made, when possible, with fresh urine. It is customary with some insurance companies to have the urine sent to a central laboratory. Boric acid is added to the urine as a preservative, and is probably as good as any, but many of the samples when examined, contain more or less of bacterial growth. It is the rule to heat such urines with strong alkali, filter and test the filtrate with heat and nitric acid. The alkali dissolves the bacterial proteins and the filtrate gives an albumin test even when there was none in the urine when passed. This accounts for the high percentage of albuminuria reported from some of these central laboratories.

The method is to be condemned. It seems difficult for some medical men to get away from the idea that bacteria are vegetable organisms. They consist mostly of protein, soluble in strong alkali, especially on the application of heat. The test, applied in the way mentioned above, gives no reliable information and is misleading. It has been suggested that the urine containing bacteria should be passed through a Berkefeld filter and the heat and nitric acid tests applied to the filtrate. This is open to two sources of error. In the first place, albumin when present may be held in the filter and thus escape detection. In the second place, some of the bacterial proteins may be in solution without the addition of alkali and may pass through the filter. —*V. C. V.*

PREPARATION of Protein Poison from Egg White.—Vaughan and Wheeler prepare the protein poison from egg white in the following manner: The whites of two dozen or more fresh eggs are dropped, with frequent stirring, into two or more liters of 96 per cent alcohol. After 24 hours the supernatant fluid is descanted and replaced by absolute alcohol. After another day, during which the coagulum is frequently stirred, it is drained into a filter, put in hulls and extracted in Soxhlet's for four days with absolute alcohol and for the three following days with ether. Thorough extraction with these reagents is necessary in order to remove all traces of saponifying substances. The contents of the hulls are rubbed into a fine powder, first in porcelain, and then in agate mortars. In this way a snow white powder of egg protein is obtained, and may be kept indefinitely in a wide-mouth bottle.

One liter or more of a 2 per cent solution of caustic soda in absolute alcohol is prepared. Care and patience are needed in this preparation. Purified sodium hydrate is needed. This should be quickly weighed, since it is deliquescent and rapidly absorbs water from the air. The broken sticks of alkali are gotten under absolute alcohol in a large porcelain mortar and rubbed into solu-

tion. This solution is diluted with absolute alcohol so as to make a 2 per cent solution.

A definite amount of the powdered egg-white is weighed out and placed in a Florence flask from which all trace of moisture has been removed by rinsing with absolute alcohol. The dry powder in this flask is covered with twenty times its weight of the 2 per cent solution of alkali. The flask is attached to a reflux condenser and to a mechanical stirrer. (The stirrer is not absolutely essential, but when not used the flask must be constantly shaken by hand.) The flask is heated in a water or steam bath for one hour, care being taken that the temperature of the contents does not rise about 78 degrees C. At the expiration of one hour the contents of the flask are allowed to cool and subside and the supernatant fluid is descanted. Three extractions of the insoluble part, with the 2 per cent alkaline solution, are necessary to complete the change of the protein into poisonous and non-poisonous fractions. The former is soluble in the alcoholic solution, while the latter is insoluble.

The combined alcoholic extracts are carefully neutralized with hydrochloric acid, which precipitates the alkaline base as sodium chloride. This is removed by filtration and the filtrate evaporated, better in vacuo. This leaves the crude poison, the action of which can be demonstrated on guinea-pigs, best by intraperitoneal, intravenous or intracardiac injection. The poison has not been obtained in a pure state and its chemical structure remains unknown. It may be partially purified from the crude product obtained as above by repeated solution in absolute alcohol and evaporation and still further by precipitation from alcoholic solution by alcoholic solution of platinum, mercuric or cupric chlorides, and the removal of the base with hydrogen sulphide. In the purest form in which it has been obtained it kills guinea-pigs with the symptoms and postmortem appearance of anaphylactic shock in dose of one-half milligram on intravenous or intracardiac injections. —*V. C. V.*

THE Preparation of Specific Precipitins.—In 1897 Kraus found that the serum of an animal which had been repeatedly treated with a culture of a given bacillus gives a precipitate when added to the filtrate of the same organism. It was soon found that this reaction is specific. Cholera serum precipitates only cholera filtrates; typhoid only typhoid filtrates, etc. Later, Tchistowitsch and Bordet demonstrated that this is a general protein reaction. A rabbit which has received small injections of horse serum furnishes a serum which precipitates horse serum in high dilution and no other proteins in like dilution. One treated with cow's milk supplies a serum which precipitates cow's milk and no other in the same dilution. One treated with egg-white precipitates the proteins of this mixture and no other in the same dilution. Practically this test is now employed in the identification of blood stains in medico-legal investigations in the detection of mixed meats and in the study of the blood relationship of species and genera. If a blood stain be dissolved in physiologic salt solution, filtered and mixed with the serum of a rabbit which has been repeatedly treated with human blood, a precipitate will form if the stain be human blood. If a hamburger steak be extracted with water the clear filtrate

will be precipitated with the blood of a rabbit which has been treated with horse serum, provided the steak contains horse meat. If the steak contains both horse flesh and beef, the extract will give precipitates with an animal treated with horse serum, also with that of one treated with ox serum. In this way the flesh of any animal, the cat, dog, etc., can be detected in the steak. This is frequently employed in municipal laboratories in Europe. The serum of a rabbit previously treated with human serum will precipitate this serum in high dilutions; that of the higher apes in less dilution and will fail to precipitate the sera of the lower apes and of all other animals. This supplies confirmation of the teaching of zoologists concerning the blood relationship of animals. The best animal for the supply of specific precipitins is the rabbit. It should receive at intervals of from three to five days intraperitoneally or subcutaneously from 3 to 5 c.c. of the selected protein and ten days after the last injection the serum of the animal is in condition to give the specific precipitin test. The substance injected into the rabbit is known as the precipitinogen (producer of the precipitin). The specific substance in the serum is known as the precipitin, and the product is designated as the precipitate. —*V. C. V.*

AGGLUTINATION.—In 1889 Charin and Roger, in studying the action of the serum of sick and immunized animals on homologous bacteria, observed that the Bacillus pyocyaneus behaves peculiarly when placed in the serum of an animal previously treated with this organism. In the serum of a normal rabbit this bacillus grows as it does in bouillon forming an opaque culture, while in the serum of an animal previously treated with this bacillus, it forms floccules which soon subside, leaving a clear, supernatant fluid. Two years later Metchnikoff observed similar behavior in the vibrio which bears his name. He wrote, "In the blood and serum of normal vaccinated guinea-pigs, the vibrio develops as it does in the ordinary liquid media, the individual organism retaining their motility and remaining distinct from one another. On the other hand, in the blood and serum of vaccinated animals the vibrios become immobile, and form smaller or larger floccules which float in the fluid."

In 1893 Issaeff, and later he and Ivanoff, observed the same phenomenon and described it as follows: "In the serum of non-immunized guinea-pigs the vibrio develops rapidly and after from four to five hours at 37 degrees, there is a uniform cloudiness throughout the fluid, while the surface is covered with a scum; but in immune serum, the microbes sink to the bottom of the tube, while the supernatant fluid remains clear. This condition continues for from eight to nine days and it is not until the tenth day that the solution becomes cloudy and a scum appears on the surface."

In 1896 Gruber and Durham demonstrated that this reaction is specific and pointed out its value in the identification of bacteria. A given bacterium is the typhoid bacillus if it is agglutinated or clumped by the serum of an animal immunized to the typhoid bacillus. This use of the phenomenon of agglutination is the only one suggested by Gruber and Durham, and it has been overshadowed by the more practical application discovered by Widal, who pointed out that it may be employed in the diagnosis of disease. If the serum of one

sick with a fever agglutinates the typhoid bacillus in high dilution the disease is typhoid fever.

The period in the progress of typhoid fever when marked agglutination is in evidence varies widely. As a rule it is not before the seventh day, but it may occur as early as the second, and it may be delayed until the second week and even later. Likewise the disappearance of the reaction after recovery is variable. It may fail ten days after the disappearance of the fever, and it may continue for years. In intensity the reaction is variable and bears no recognizable relation to the severity of the disease. The method of applying the test, as recommended by Widal and Sicard is as follows: "A number of small diameter tubes, each containing 1, 2, 3, 4, and 5 c.c. of bouillon are kept on hand. When a test is to be made, one adds a drop of the serum to each of these tubes and then inoculates each with a typhoid culture. The tubes are then placed in the incubator for from four to six hours. At the expiration of this time it may be seen at a glance in which tubes agglutination has taken place, since these will be unclouded and the floccules will be seen at the bottom. The first tube is a dilution of 1:20, the second 1:40, etc."

Johnston showed that a drop of blood allowed to dry on non-absorbent paper may be transported any distance and kept indefinitely and still be capable of giving the agglutination test after solution in water, but this does not permit accuracy in determining the dilution. Agglutination may be observed under the microscope when only one drop of blood is available. When serum is sent to a distant laboratory for examination formaldehyde may be added, but a preservative is not necessary, since putrefaction does not interfere with the test. A positive diagnosis should not be made unless marked agglutination is observed in a dilution of not less than 1:50, and even in this dilution there is chance for mistake. In experimental animals sera can be obtained which will agglutinate typhoid bacilli in dilutions as high as 1:1,000,000 and colon bacilli 1:2,000,000.

In the identification of bacteria agglutination should take place in high dilutions, which, however, vary with the organism. The strongest proof that Shiga's bacilli is a cause of dysentery lies in the fact that its cultures are agglutinated with high dilutions of those ill with dysentery.

—*V. C. V.*

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EDITORIALS

The New Journal

WHY start a new medical journal? This question will arise in the minds of all who see this publication. It is a perfectly proper question and one which we have asked ourselves many times in the past few months. It does seem that the medical profession is already oppressed by a great flood of literature, some good, some bad, and much of it indifferent. There are general and special organs, weekly, monthly and quarterly, in all the languages of the civilized world. Then why start another? Why ask the medical man to add another to the great heap of periodicals that—often unopened—burden his table? To these questions we have given serious consideration and finally have decided that a medical journal, of the kind which we hope to make this, will be of value to the profession. At present there is a wide chasm between the research man and the practitioner. The former mines the ore, the latter refines it and shapes it into useful implements. The work of the one supplements that of the other. The world is not benefited nor medicine advanced until the work of both has been done. Modern medicine consists of those facts gathered from the various sciences which may be utilized in the prevention or relief of disease. Scientific discovery must precede practical application, but until the proper use is found the value of the discovery is wholly potential. The basic aim of this journal will be to bring discovery and its application closer together, to supply the research man with a strictly scientific organ through which he can report the results of his labors, and to suggest to the practitioner how he may use the latest discoveries. The journal will be filled with original

articles and editorial reviews. In the former we hope to present much of the best productive research done in this country. In the latter there will be a record of the advances in the physical, chemical, and biological sciences, so far as they have medical significance, made by experts. Contributions to the physiology, nutrition and life phases of man, discoveries in etiology, pathology, and the development of disease processes, improved methods of diagnosis and treatment will be reported, and the endeavor will be to keep the practitioner close upon the heels of the discoverer. The man who relies upon text-books to keep up with his profession today is falling far behind in the race. Special scientific periodicals are numerous and of these our own country is now producing some of the best, but the practitioner can hardly be expected to read any large number of these and there is certain benefit to the profession in having much of the work reported in these special organs gleaned and made readily comprehensible. Mere abstracts without proper interpretation are of but little value. We propose to review original work especially that which will be of either intellectual or practical value to the practitioner. These reviews will be accompanied by comments and possibly by criticism from the reviewer. Abstracts of scientific contributions by those not well informed as to what others have done along the same line are of but little value. The editorial staff has been selected with the intention of having an expert present with proper estimate the results of the latest scientific investigations. Only those expertly trained can properly interpret work of this kind.

The man who attempts to practice medicine without laboratory aid belongs to a past generation, and fails to do justice to his patients or credit to himself. Our purpose will be to present the work of our best investigators to the practitioners, either directly in the form of original contributions or as reviews of work published elsewhere. One of the most encouraging evidences of the scientific advance of medical practice in this country is the increasing appreciation and utilization of laboratory methods in diagnosis. Without proper diagnosis treatment fails and in a large per cent of the cases coming to the practitioner the former is quite impossible without the aid of the laboratory. Our endeavor will not be limited to curative medicine, but will include much in the art of the prevention of disease.

The ultimate goal of science is the domination of the forces of nature and their utilization in the betterment of mankind. In this great work the medical profession must play an important part and it is our one desire that this journal may aid in carrying on this work. —*V. C. V.*

Phagocytosis

IT has been assumed for many years that phagocytosis is an active process, and that it is associated with the power of active motion in certain cells. These cells send out projections from their bodies toward certain particles which happen to be present in their environment and presently surround them, and in certain instances destroy them. In the process of phagocytosis, chemical reactions have always been given a prominent place, for it has been held that certain variations in chemical reactions in some way account for the move-

ments of cells (chemotaxis). A recent communication by Oliver[1] discusses the crenation and flagellation of erythrocytes and throws some light upon the process which is responsible for amœboid activity of cells. Crenation is apparently the opposite of flagellation and can be produced entirely by physical means. For instance, Oliver shows that if one takes a crenated blood corpuscle and merely touches it with a fine glass needle, which is immediately withdrawn, the cell becomes round again and appears optically normal, and remains so. If, on the other hand, a glass needle is brought close to a normal red corpuscle, but not touching it, it immediately crenates, and the degree of crenation depends upon the proximity of the needle to the cell. By following the physical method of Oliver, cells may be crenated and uncrenated at will and more or less indefinitely. Since the phenomenon of crenation has always been attributed to hypotonicity of the surrounding fluid, it is interesting to note that the phenomenon can be produced regardless of the tonicities—that it occurs equally well in isotonic, hypotonic, or hypertonic solutions. The phenomenon of crenation seems therefore to depend upon conditions of surface tension which are produced in making the ordinary mounts of fresh blood, and it illustrates the extreme irritability of cellular protoplasm. Oliver continues with some observations on flagellation which were suggested to him by Kite's work. He noticed that soon after making fresh preparation of blood, many of the cells were crenated, and that some 40 or 50 minutes later the cells were seen to possess long processes, some motile and some non-motile. By means of such motile process the cells are moved across the field of the microscope. These processes may become free from the cells and show independent motion. Non-motile processes may be made to beat by merely touching them with a fine needle held in the Barber holder.

These observations lead very directly to those of Kite and Wherry[2] upon the mechanism of phagocytosis. They suggest that phagocytosis depends upon the physical conditions of the surface of the phagocytic cells and that the engulfing of particles is a purely passive process which depends upon protoplasmic streaming within the cells. They believe that such substances as opsonins act in increasing phagocytosis merely because they increase the "stickiness" of the cells, and that phagocytosis depends essentially upon the relative stickiness of phagocytes and bacteria. Their experiments indicate that the physical manipulations invoked in making opsonic preparations are sufficient to account for the part of the phenomenon of phagocytosis in such preparations, and that bacteria stick to the phagocytes best in the presence of unheated serum because of the presence of something in the serum which makes them more sticky. Incubation of specimens following the Wright technic for determining the opsoninic index seems, from these experiments, to be valueless, for the phenomenon will occur at any temperature from 11 degrees C to 37 degrees C. The process of mixing is important, for a very careful, quiet, technic reduces phagocytosis.

A recent report by Lawson[3] adds emphasis to the work of Oliver, and Kite and Wherry. Miss Lawson shows that contrary to the current conception, the malarial parasite is not intracellular, but extracellular and perhaps pericellular. They become attached to the erythrocytes at certain points which are referred

[1]Science, 1914 (40) 645.
[2]Journ. Infect. Dis., 1915 (16) 109.
[3]Journ. Exp. Med., 1915 (21) 584.

to as "mounds" which the parasites tend to surround with pseudopods. Here again is evidence that mechanical contact produces changes in the contour of the red cells and that at the same time the relative stickiness of the protoplasm of cells and parasites is increased so that they adhere to one another.

Upon the basis of these researches which indicate that purely physical forces are of first importance in explanation of phagocytosis, the older work upon which our current accepted conceptions are based, must be repeated, and interpreted from a new angle. —*P. G. W.*

*Recent Work on Blood Pressure Measurements in Man**

IT would seem a comparatively simple problem to ascertain, by laboratory experiments, the actual pressures in the blood streams at which changes, that are similar to those observed in making blood pressure measurements in the clinic, occur in the behavior of the pulse, when varying outside pressures are applied to the artery. Connecting a mercury manometer with a branch of the artery on which the "clinical" methods are being tested, and then comparing the readings taken by the two methods would appear to be all that is necessary in order to test the reliability of the clinical method. But unfortunately the information thus obtained has been of only limited value, because the dissimilar anatomical relationships of the vessels in laboratory animals and in man introduce physical differences which alter very considerably the behavior of the pulse. In view of these facts, and because of the enormous practical importance to the clinical observer of knowing just exactly how reliable are the methods at his disposal for gauging the blood pressure, two eminent physiologists, Professor J. A. MacWilliam, of Aberdeen, Scotland, and Professor Leonard Hill, F.R.S., of London, along with several collaborators, have been, and are at present, engaged in throwing further light on the question. In the following review we shall summarize the main findings of these workers, in so far as they would seem to be of value to the clinical worker.

There are three aspects of the arterial blood pressures which it is important to measure, the *systolic pressure*, the *diastolic pressure*, and the *pressure pulse*. The first means the high pressure attained in the blood stream during each heart beat, the second, the lowest pressure occurring between the heart beats, and the third, the difference between the systolic and the diastolic pressure. A fourth value—the *mean blood pressure*—is the average between systolic and diastolic pressures. Each of these is given in terms of the height in millimeters of a column of mercury, and in the brachial artery of a healthy young man while lying down they usually amount to 115 m.m., 85 m.m., and 30 m.m., respectively.

Before proceeding to review the actual methods of measurement it will be well to consider the *practical value of the results in elucidating the actual conditions in the circulation.*

(1) *Systolic Pressure:* Even when the systolic pressure is accurately measured—and we shall see shortly that some care has to be exercised in do-

*For convenience this editorial has been divided into two parts, the second installment to appear in the November issue. The literature is given at the end and is referred to in the context by numbers.

ing this—"it gives very insufficient evidence as to what is going on in the circulation," for all it tells us is the momentary highest pressure transmitted to the blood column by each heart beat.[5] Thus, in heart block the systolic pressure may be very high and yet the mass movement* of the blood quite defective, as evidenced by symptoms of cerebral anæmia; or again, in cases of slow cardiac failure in which cyanosis, dyspnœa, etc., are pronounced, the systolic pressure may be about the normal level.

(2) *Diastolic Pressure:* Measurement of the diastolic pressure is important not only because it gives us the load which the vessels and the aortic valves must constantly bear and the resistance to the opening of these valves at the beginning of systole, but because it helps us to gauge the peripheral resistance. In using the diastolic pressure for this purpose, however, it must be remembered that the heart rate also affects it, a slow beat making it fall and a quick beat making it rise. It is therefore possible to have a normal diastolic pressure, either with a low peripheral resistance and a quick pulse, or with a high peripheral resistance and a slow pulse. In these cases the arterial walls may be perfectly healthy. When the walls of the arteries are stiffened, the diastolic pressure becomes lower (if they were perfectly rigid the diastolic pressure would be zero). In such cases, however, the pressure pulse will be very marked. A high diastolic pressure in cases with stiffened arteries, and no quickening of the pulse, is very significant of a high peripheral resistance. It is of great practical importance to remember that a constantly high diastolic pressure entails a much greater strain on the vessel walls than the transient systolic pressure, and should be taken as a danger signal of possible rupture.

(3) *Both Systolic and Diastolic Pressures—Pressure Pulse:* Can we assume that with normal systolic and diastolic pressures, and a normal heart rate, the circulation is normal? In the vast majority of cases we can, but not always. Thus, in cases where the aortic orifice is narrowed, so that less blood is discharged during systole into the vessels, we may at the same time have a narrowing of peripheral blood vessels, thus increasing the resistance to outflow and compensating for the deficient cardiac output, so that the above pressure readings are normal. But obviously, under these conditions the mass movement of the blood must be deficient, as is frequently evidenced by the general symptoms of dyspnœa, pallor, cerebral anæmia, etc., so common in aortic disease.

These facts will make it plain that although the estimation of *both* systolic and diastolic pressures is of very great importance and value in clinical diagnosis, yet "they must on no account be regarded as superseding or rendering unnecessary the use of other sources of information regarding the condition of the circulation. . . . Error from misuse of the results of blood pressure estimation, by blind adherence to mechanical standards, is easily avoided by common-sense application of other obvious signs taken in correlation with the blood pressure data." (MacWilliam.[5])

The Measurement of the Systolic Pressure: Auditory, visual and tactile methods exist for the measurement of the systolic pressure. In all of them an armlet is placed around the arm or leg and the behavior of the pulse is exam-

*By mass movement of blood is meant the volume of blood which passes a given point in the circulation in a given time. Volume flow means the same thing.

ined, by one or other of the above methods, lower down when the air pressure in the armlet (which should be 12 c.m. broad) is raised and lowered by means of a suitable pump. In the *auditory method,* a stethoscope or phonendoscope is placed immediately below the armlet. When the pressure in the armlet is raised above the systolic, no sound is heard, but on gradually decompressing, a distinct tapping sound becomes audible with each heart beat. This indicates the moment at which blood begins to force its way, during systole, along the vessel beneath the armlet, and the pressure now registered by a manometer connected with the armlet is taken as the systolic (systolic index). We shall explain immediately how, on further lowering the armlet pressure, the diastolic pressure is indicated.

The *tactile* method consists in palpating the radial, or dorsalis pedis, or posterior tibial arteries. No pulse is palpable until the armlet pressure has been lowered to a few millimetres below the auditory systolic index. This tactile systolic index is, therefore, always below the auditory; if it is not so, it indicates that some error has been made in the application of the apparatus, most usually in the phonendoscope. If readjustment does not bring the two "indices" into proper relationship, the auscultatory method cannot be relied upon, either for systolic or diastolic readings (MacWilliam[5]).

The *visual* method consists in watching the pulsations in the manometer connected with the armlet. With pressures above systolic very faint, if any, pulsations are visible—this depends on the delicacy of the manometer—but when the pressure is lowered to the systolic, the pulsations become more pronounced.

Of course, each of these methods can be employed while the armlet pressure is being gradually raised instead of lowered, but the readings are often different and we shall have to consider later the reasons for this.

Meanwhile there are several *conditions affecting the gauging of the systolic pressure* which we shall have to consider.

A. The Mode of Compression of the Artery: Leonard Hill and his collaborators[6] have found that there is an extraordinary difference in the amount of pressure required to obliterate an artery, so that no recognizable pulse occurs below, according to whether the vessel is compressed with or without at the same time compressing the tissues in which it lies. This has been shown both clinically and experimentally. Thus, when the small bag of the pocket sphygmometer (Leonard Hill's) was placed on the radial artery, embedded in the tissues of the forearm, a systolic pressure of 110 m.m. Hg. was observed, but when applied a little lower down to an aberrant radial, the pressure was only 35 m.m. Hg. Similar differences can be demonstrated in the leg vessels and the dorsalis pedis. Experimental corroboration of these clinical findings was obtained by exposing an artery in a living animal: when this was compressed in a tube full of saline, the pulse, distal to the compression, was not obliterated until the pressure was raised just above the systolic pressure of the blood in the artery, whereas when the same artery, placed on bone, wood or glass, was compressed locally, as by arranging an armlet so that it did not embrace other tissues, the pulse was abolished by pressures that were not only considerably under systolic but even under the diastolic pressure. For accurate

systolic readings it is therefore very important to use an armlet which is at least 13 c.m. wide.

B. Discrepancies between Systolic Readings on Compression and Decompression of the Armlet: The pulse below the armlet may reappear on decompression at a lower pressure than it disappears on compression. This discrepancy is most marked when the decompression is done quickly. By means of a circulation model, the general construction of which will be described later, Hill and his collaborators[7] have succeeded in demonstrating that the above discrepancy is due to the fact that the full force of the pulse does not reach the forearm until all the vessels of the upper arm have become filled with blood and therefore tense. This explanation was further corroborated by finding that it took much longer than usual for the pulse to return at the wrist on decompression when the forearm had been emptied of blood, by elevating it and applying a bandage before compression and then removing it just before decompression.

C. Discrepancies in Systolic Readings from Different Limbs: It is not uncommon to find that the systolic pressure in the leg is higher than that in the arm, even when the patient is in the horizontal position. It is particularly in cases of *aortic regurgitation* that the discrepancy is seen. Hill, McQueen and Flack[6] have made extensive investigation of the causes for this difference and conclude that it is partly due to: (1) The greater lumen of the aorta, iliac and femoral arteries in comparison with that of the subclavian and brachial; the wider the lumen, the greater the amplitude of the pulse wave. (2) The pulsating support which the relatively massive abdominal organs and the tissues of the thigh give to the main arteries prevents the damping of the crest of the pulse waves. (3) The leg arteries are probably held in a more supported state, and are less labile than the arm arteries, so that the pulse is conducted to the leg with less diminution in force. As an outcome of experiments with artificial models, already referred to,[8] these same authors place emphasis on the last of the above explanations; to quote, "The explanation of the difference which pertains between the arm and leg systolic readings taken in the horizontal posture, in cases of aortic regurgitation, is to be sought in the difference of the lability of the artery and the condition of the peripheral circulation."

Similar discrepancies in systolic readings between different limbs are also observed, especially on the first estimation of the pressure, in cases with *thickened arteries.* MacWilliam and Kesson[2] have made an extensive investigation of the observed pressures in such cases, and have found that the discrepancy becomes greatly reduced on continued or repeated compression of the artery, and that the fallacious reading (i. e., the one that is high) is decidedly less when the pressure of reappearance rather than that of disappearance of the pulse is measured. It is pointed out, however, that the repeated compression of the hardened vessel may introduce a fresh complication in the gauging of the pressure, on account of the rise in general blood pressure. By investigating the behavior of fresh surviving arteries in different conditions of contraction and relaxation in a circulation schema (see below), it was found that repeated compression caused the contracted artery to behave, qualitatively at least, like the normal artery. The extraordinary degree of change in pressure sometimes ob-

served in the artery embedded in the human limb after continuous pressure could never be duplicated in excised arteries unless these were extremely contracted (such as pathological arteries from the legs of horses, or arteries artificially contracted by barium chloride), arteries, that is to say, which are very much more contracted than is ever possible in the human limb. The explanation offered by MacWilliam, etc.,[5] for this peculiar behavior of the arteries is along the lines suggested long ago by von Recklinghausen, namely, that the hypertonic artery when compressed externally does not, as does a normal vessel, become completely closed, but its walls become apposed at the middle part while chinks still remain at the sides. The blood continues to pass by these chinks, and to obliterate them a very considerably higher arterial pressure is required. By continued or repeated compression it could be shown, in excised hypertonic arteries, that the tonic contraction was temporarily removed so that the walls of artery become apposed in normal fashion. If this is the true explanation of the different systolic pressures often observable between the arm and leg arteries, it should follow that, although the pulse does not disappear in the leg at as low a pressure as in the arm, there would be some demonstrable change in its character at the pressure at which it disappears from the arm. Such was found to be the case in a patient showing an obliteration value (i. e., systolic index) of 115 for the upper arm and 198 for the leg; "at 116 the pulse in the leg though not obliterated was very notably cut down in volume; it persisted as a pulse of small volume with very little alteration till it became obliterated. . . . Repeated compression was tried and was found to give marked lowering in the leg readings at successive tests, namely, 198, 186, 168, 149, 148 m.m." During all this time the arm pressure remained steady at 115 m.m. The differences were much more marked when the calf vessels were used than with those of the thigh.

Besides these abnormal cases of aortic disease and contracted arteries, we may find even with *normal vessels* that the systolic measurements, taken at different parts of the circulation, do not agree; more especially after muscular exercise. Thus, Hill, etc.,[7] state that the systolic reading in the thigh is considerably above that in the calf in normal boys, such readings as the following being reported in these different cases:

Thigh	*Calf*
165 m.m. Hg.	135 m.m. Hg.
155 " "	120 " "
105 " "	80 " "

In other cases (designated as patients, however, see footnote on p. 510, *loc. cit.*) the readings were considerably higher in the calf than in the thigh, and the differences could not be accounted for as due to protection of the artery from compression by fasciæ, etc.

D. Increase in Pulse Beat at Wrist at the Beginning of the Rise in Armlet Pressure: When an armlet is placed on the upper arm and the pulse is felt at the wrist, the latter will often increase perceptibly in force as the armlet pressure is raised from zero to 50 m.m. Hg.[7] In some persons this, seemingly paradoxical, behavior is very pronounced; thus, in a patient whose systolic pressure was 130, and diastolic 80 m.m. Hg., the increase in force of the

pulse became perceptible when the armlet pressure was raised to 36-40 m.m. Hg., but when the same patient did muscular exercise, and so caused the difference between the systolic and diastolic pressures to become greater (i. e., increase of pressure pulse), the increase in the pulse was observed with 10 m.m. of pressure in the armlet. In aortic disease also, where there is a similarly large pressure pulse, even during rest, the augmentation on the radial pulse was apparent with 5-10 m.m. armlet pressure. Similar augmentation of the pulse in the calf was obtained during increase in the pressure of an armlet placed on the thigh.

Not only can the augmentation of the pulse be felt by the finger, but it may be demonstrated by using a sphygmograph. It is also associated with the appearance of a distinct sound heard by listening over the artery with a stethoscope or phonendoscope.

When we come to describe the method by which the changes in pulse sound may be used for measuring the systolic and diastolic pressures (see below), we shall see that, starting with a high armlet pressure and gradually lowering it, no sound is heard until some blood succeeds in passing the armlet during each systole. As the pressure is lowered, this sound gets louder, until at a certain armlet pressure, which corresponds to the diastolic, it suddenly gets less. At lower pressures it still persists for a time, and the pressure of its final disappearance is that at which the described augmentation of the pulse is perceptible. Thus, in the patient already referred to above, there was no sound discernible at the elbow until the armlet pressure had reached 30-40 m.m. Hg., although after muscular exercise it became evident at 10 m.m. In entire conformity with these findings is the well-known clinical experience that in case of aortic disease a pulse sound is heard over the arteries without any armlet pressure at all. This sound becomes more marked with slight armlet pressures.

The cause of the sounds is ascribed by Hill, etc., "to the impact of the systolic wave vibrating the tense artery and its branches. . . . This sets the mass of tissue enclosed in the armlet into vibration, the vibrations becoming audible to the ear as sounds. . . . Therefore, the sound is dependent on the pulse-pressure range of the blood stream which enters the armlet. . . . If the pressure within the armlet is raised, the systolic wave is reinforced by the increased tension of the arteries under the armlet, and the sound becomes louder."[8]

A very interesting simple experiment corroborating this explanation of the sound (viz., that it is due to the sudden tension produced by each systole on vascular tissue under the cuff), consists in placing two armlets around the arm with a phonendoscope between them. When the pressure in the upper armlet has been raised sufficiently to make the sound audible, inflation of the lower armlet to a pressure above the systolic does not cause the sound to disappear, but rather to increase. Complete stoppage of the circulation does not, therefore, diminish the sound, thus indicating that it must be due to tension changes in the vessels.

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[8]Do.: II. A Schematic Investigation. Ibid, pp. 516-536 (1915).

—*J. J. R. M.*

The Constituents of Dietaries—A Review

OSLER has said that the physician who wishes to obtain a sound knowledge of the natural history of disease, must adopt Morgagni's method of "anatomic thinking." It is becoming more and more evident that the modern physician must go beyond this and adopt the method of physiologic thinking, and he should remember that this implies physical and chemical thinking. The medicine of the present is based more largely than ever before upon the fundamental sciences, physics and chemistry and the evidences are that these sciences will play an ever increasing role. The "method of Zadig" (or of Morgagni) is the observational part, but under this, furnishing the foundation for logical diagnosis, prognosis, and treatment, is pure chemistry.

Nowhere in the literature is this point of view more clearly illustrated than in the reports of investigators dealing with the influences of diets. These reports form two general groups, those which, like the ones of Schaumann, Funk and others, deal with certain diseases like beriberi and scurvy; and the ones of Osborne and Mendel, and others, which have to do with the effects of dietary re-arrangements and limitations in experimental animals, and the relationships of the items in the diets to growth.

There are, of course, two sides to the question of diets. The state of nutrition of an individual is dependent upon certain conditions in the external world, such as the quality and quantity of nutritive material which is available, and also upon the internal structure of the body upon which is dependent the powers of the individual to make use of food. It makes no difference how much food nor how good food is available to an individual if his tissues are not able to assimilate it, nor does it matter how *well* the body is, if the food supply is not sufficient in quantity and quality,—he starves just the same. In one case he may not grow,—which is partial starvation.

It may be trite to call attention to the fact that the amount of food that is necessary for an individual, depends upon his age, the amount of muscular

activity he displays, the climate (or the weather), and certain other factors such as the activity of one or more of the ductless glands, as well as indefinite and not-understood ones which we group together as "inherited." Everyone realizes the atrociously large appetites of children who are active, but one sometimes forgets that the dosage of milk which is accepted for a six-months' child is for the average hospital child and not (necessarily) for the healthy, active child that would grow faster if it had more food. One knows that what is needed in hot weather is food enough, and plenty of water to counteract the heat produced in burning the food. The value of peppers in the tropics is that (given enough water) perspiration is stimulated and the result is cooling.

If the normal amount of food is consumed and if the food is used by a normal body, physiologic growth will occur. But if too much food is taken, or if the body is inactive, food will be stored in the form of fat. Lack of exercise is the great cause of obesity. That is why, in part at least, the contented person tends to stoutness, for other things being equal, the contented person "rests" more; his mind and muscles are oftener at ease and so he burns less of his food. "Laugh and grow fat" is a physiologic truth. But many adipose persons are not contented, and many are very active. In such cases one of two things is apt to be wrong,—either they have inherited a type of metabolism which is not normal for the race, or something is wrong with his organs of internal secretion—especially the pituitary, the thyroid, or the sex glands. Similarly the thin individual is one who eats too little, or exercises too much, or is nervous; who has some ductless gland disorder, or who is "just naturally skinny."

But even so, we have looked at but part of the picture. We have taken for granted that the food is good in *quality*. An individual must have, not only good food, but the composition of the food must be proper. The diet must contain a certain proportion of protein, of fats, of carbohydrates, and of salts, beside the right amount of water.

It has been known for a long time, that if enough protein is not eaten the body suffers, and something like the same thing has been known of the other dietary constituents. The seafaring people learned that salt meat and bread would not keep a man alive and well, even though it contained the theoretically proper food values. Such a diet produces scurvy. If mere boiling of milk for babies reduces its value as a food, it is not because the *food values* are not there, but because certain constituents are physically changed.[1] Frank[2] has offered evidence, for instance, that the digestibility of egg-white is influenced by the temperature at which it is coagulated. A diet of certain kinds of rice, which are lacking in phosphorus and perhaps other substances produces beriberi in the tropics; and a diet of dried grain (oats) and water produces a disease like rickets or scurvy in guinea-pigs. A little fresh food, *living food*, such as salad, or fresh milk, or even merely milk whey, will correct such diseased conditions. It is probable that pellagra is one of the diseases caused by unbalanced or deficient food. It is an interesting fact that the substances which will correct some dietary defects are active in such small amounts that they

[1]Compare with Rupp: Bull. 166, Bureau of Animal Industry.
[2]Journal of Biolog. Chem., 1911 (9) 463.

can scarcely be detected. They are called collectively for the present the "vitamines." Funk[3] has suggested that these substances have a certain relation to the activities of the glands of internal secretions.

Since a balanced diet must be composed of more or less certain amounts of protein, fat, carbohydrate, salts and water, it is obvious that an inadequate diet may be deficient in one of several ways,—it may lack any one of the necessary constituents, or it may lack more than one. It is interesting that we have come to know, of recent years, that the lack may be not merely a gross one, as exemplified in absence of proteins, but it may be a chemical one and dependent upon the structure of the protein. Perhaps much the same state of affairs exists in regard to the fats and carbohydrates, perhaps also to the salts.

A great deal of our newer information concerning the proteins we owe to Osborne and Mendel.[4] They have experimented with pure proteins and have shown definitely that certain amino acids are indispensable in food. With certain proteins, lacking certain amino acids, maintenance, but not growth, occurs. With other proteins lacking certain other animo acids, not even equilibrium can be held. For instance, they have shown that the protein of corn (zein) is an inefficient protein, and that when zein serves as the sole source of nitrogen in a diet nutritive failure results. It is a perfectly digestible protein but lacks tryptophan and lysin. The addition of both these latter to zein completes it. Add tryptophan alone and equilibrium is maintained; add both, and growth follows. Gelatin is not an efficient protein because it lacks tryptophan. Also they have shown that the protein of wheat (ghadin) which will serve in maintaining equilibrium, will not permit of growth, but add lysin to gliadin, and growth results. Gliadin is evidently a better source of nitrogen than zein. Lysin is present in many foods, for instance, 8 per cent in lactalbumin; 7.59 per cent in ox muscle; 4.81 per cent in egg yolk; 4.98 per cent in peas; and 4.58 per cent in beans; 7.61 per cent in casein. The addition of any of these to a corn or wheat dietary (in which connection one thinks of breakfast foods) adds to its efficiency, and tends to insure growth. These facts apply to adult animals to be sure, but they apply more trenchantly to young animals.

Osborne and Mendel have also added much to our knowledge of the food value of fats.[5] They found that young animals (rats) did not complete their growth upon a diet of isolated proteins, starch, protein-free milk and commercial lard or olive oil, but if butter fat replaced the lard, growth went on. They also found that cod liver oil could be substituted for the lard. McCollum and Davis,[6] and Osborne and Mendel have also found that if egg fat is added to a lard containing dietary, growth will occur. Evidently the type of fat in a diet is important also.[7]

Little is said in the literature regarding the influence of carbohydrates.

[3]Journ. Physiol., 1914 (47) 475.
[4]Osborne and Mendel: J. Biol. Chem., 1914 (17) 325; 1914 (18) 1; Med. Record, 1914 (85) 737; cf. also Jour. A. M. A., 1914 (63) 190.
Mendel: Jour. A. M. A., 1914 (63) 819.
[5]Osborne and Mendel: J. Biol. Chem., 1914 (17) 325; ibid., 1914 (18) 1; cf. also J. A. M. A., 1914 (63) 190; Med. Record, 1914 (85) 737.
Osborne and Mendel: J. Biol. Chem., 1913 (16) 423; Ibid., 1914 (17) 401; ibid., 1912 (12) 81.
[6]McCollum and Davis: J. Biol. Chem., 1913 (15) 167.
[7]Mendel: Jour. A. M. A., 1914 (63) 819.

Evidently their chief function is to furnish the sources of heat for the body. They do not form an indispensable part of the dietary so far as growth is concerned. They seem to be more or less alike. Any of the common carbohydrates may be efficient. The usual one used in experimental diets is starch. It appears, however, from the recent experiments of Tachau[8] that an addition of sugar to an already adequate diet may result disastrously—how, one cannot say. Tachau obtained similar results with certain salts, and fats. It is possible that the easily burned carbohydrates may, under certain conditions, furnish too much heat; then, unless the windows are opened, the house may get too warm, or they may, in too large quantities be incompletely burned and produce substances which interfere with protoplasm (cellular) chemical processes (cellular asphyxia). The split products of both carbohydrates and fats may indeed menace the body, and lack or over-abundance of salts may surely change the reactions of the living cells. In interpreting the results of experiments, one may bear in mind that the "living organism may be regarded as a highly unstable chemical system which tends to increase itself continuously under the average of the conditions to which it is subject, but undergoes disintegration as a result of any variation from this average."[9] There seems to be no evidence that in the so-called *Mehlnährschaden* the starch itself is the harmful agent. It is only when given in excessive amounts for long periods that harm results, and this is due not so much to the starch as to the attendant deprivation of other food stuffs.[10]

If an animal is fed upon a diet consisting of the proper amounts of protein, fats, carbohydrates, and water, with no salts, it will die more quickly than if it received no food at all.[11] The importance of salts has been dwelt upon by various workers, but no one has shown in simpler way, or in a more convincing form, the reasons for the value of salts in the economy than M. H. Fischer.[12] It seems to be true that the importance of various salts in the human organism is due to their effects upon the physical condition of the proteins of the body. They furnish practically no energy and yet are essential. Schaefer[13] has said that the chemistry and physics of the living organism are essentially the chemistry and physics of the nitrogenous colloids, and Guyer[14] wrote that what we call protoplasm "is really an aggregate of colloids holding water for the most part, in which are contained certain salts and non-electrolytes."

These salts, it seems, are of intrinsic value because they change the affinity of the protoplasm for water, so that at one time when there is a relative lack of salts, the protoplasm loses water, and at another time they absorb water, and with it, food materials. In other words, we may suspect that the salts of the food are the agents which control to a large extent secretion and absorption. Certain salts, of course, are regulators of neutrality in the body, but that is but a part of the problem of secretion and absorption.

[8]Tachau: Biochem. Ztsch., 1914 (65) 253.
[9]Starling: Human Physiology, 1912, p. 5.
[10]cf. Abt. Jour. A. M. A., 1913 (61) 1275; also Grafe: Deut. Arch. f. Klin. Med., (113) 1.
[11]Starling: Human Physiology, 1912, 724.
[12]Fischer: Oedema and Nephritis, 1915.
[13]Schaefer: Science, 1912 (36) 289.
[14]Guyer: Trans. Amer. Micros. Soc., 1911 (30) 145.

All of the various salts have perhaps different values in the economy. In Osborne and Mendel's experiments, the salts of sodium, calcium, and magnesium were used in the form of chlorides and phosphates, which indicate from the outcome of their work that these are the more important ones.

Certain salts such as many of the organic acid salts (citrates, for instance) act as alkalies in the body. They are diuretic and cathartic and this action is the result of withdrawal of water from the tissues. It is comprehensible that such salts tend to over-alkalinize the tissues. Salts of the inorganic acids on the other hand, tend to over-acidize the tissues when used in more than sufficient amounts.

The role of salts, while not sufficiently elucidated, has played some considerable part in medical literature. It has been held that goitre, pellagra, beriberi, scurvy, rickets, etc., are in part, or as a whole, dependent upon the content of the diet of certain salts. In no case has the proof been brought. Recently it has been suggested[15] that (in the case of pellagra) the salts of silica are the active cause, but that the silica must be in a colloidal form.

Most interesting of all the suggestions, are those which have come of recent years and which concern themselves with the so-called vitamines.[16] These substances cannot be classed as yet with either proteins, carbohydrates, fats or salts, though it seems possible that they may be salts in a colloidal state. Cooper[17] is inclined to believe that these substances, formerly referred to as "antineuritic" are neither proteins, fats, or lipoids, and there is no evidence that they are carbohydrates. The term as first used by Funk was applied to certain substances of undetermined structure which occurred in the outer parts of grain. (It is this part which is removed during the polishing of rice.) It has been suggested that there are different vitamins which are active in preventing disease—one for beriberi, one for scurvy, one for pellagra, etc. They are present in food stuffs in such exceedingly small amounts that they cannot, it seems, have any caloric value and yet they seem to be essential. It has been suggested that they are in some way united with the part of the food in which flavor resides.

There seems to be but one general way in which to formulate the diet question, bearing in mind the fact that "a man who maintains his weight may be in excellent nutritive condition, but a child who does the same thing, is failing to grow."[18] Each individual needs a different amount of food, which will vary according to his structure and surroundings; he will need protein, carbohydrate, fat and salts, in addition to water; he will need certain types of proteins, certain types of fats, and certain salts; and finally he may need other substances, which have perhaps to do with flavor, called generically vitamines, if he is to show physical growth.

[15]Cencelli: London Lancet, Apr. 17, 1915.
[16]Funk: Die Vitamine., Wiesbaden, 1914.
[17]Journ. Hyg., 1912 (12) 436.
[18]Osborne and Mendel: Carnegie Inst. Publication 156, 1911.

—*P. G. W.*

Variations in the Rate of the Heart Beat

QUESTIONS relating to the pulse rate (and the heart rate) are of ever-continuing interest, and everywhere clinicians discuss with eagerness the variations in the heart beat and attempt to draw conclusions which may be more or less valuable in proportion to the knowledge of the clinician of the physiology of the heart. It deserves saying that, even in the case of the most careful man, the knowledge will be limited because so little is known of the cause of the cardiac (and therefore the pulse) rate.

There are, however, a certain number of data that it is well to consider in discussing the pulse rate. First of these, is the fact that from the tacchycardiac pulse of the infant there is a gradual decrease with age, from about 130 at birth to 85 at about the twelfth year, with a further decrease to an average of about 70 at twenty years. This average remains fairly constant up to say 50 years, after which time there is a slight increase. All this means is that there are *age variations* in the pulse. Chotak refers to these variations as growth period changes, and suggests that they correspond to a gradual increase of vagus tone. Perhaps they are due to changes in the motor functions of the heart. The difficulty with this idea is that we do not know what "vagus tone" is, nor what "changes of motor function" are.

Again there are individuals whose average pulse rates and heart rates are above, in some instances, or below, in others, the so-called normal average. There are persons who have a constant rate of 100. There are also persons whose rate is constantly below 70. Since the cause of the normal rate is not known, one can only surmise as to the cause of the variations. In certain cases there seems to be an anatomic basis for the tacchycardias or bradycardias. Michailoff, for instance, found a neuroma in the dorsal cord of an individual who had shown a tacchycardia since childhood and who lived to be 62 years old. In this case the cardiac rapidity may have been due, as Michailoff suggests to a mechanical pressure effect upon accelerator fibres, or it may have been due to some other factor.

Again there are differences in heart rate connected with sex, size, temperature (Loeb and Ewald), time of day and relation to meals (Weber), posture, etc. Geigel observed an average loss of 12 beats during recumbency and suggested that this was the result of increased cerebral pressure and vagus irritation.

In this connection the observations of Klewitz are exceedingly interesting. He observed an average loss of cardiac frequency of 19.9 per cent during sleep. He believes that this loss which may be greater under perfectly quiet conditions is the result of cutting down of afferent nervous impulses from the environment. He also says that a heart in which there is a compensated valvular lesion acts like a normal heart in respect to its recumbency losses, and that in decompensated the losses approach the normal in direct proportion as the lesion is compensation;—in other words, that the percentage decrease serves as an indicator of the degree of decompensation. In severe cases of cardiac decompensation the pulse rate during sleep may run above the waking normal. Such a heart cannot recover its tone during sleep as does a normal or compensated heart.

A considerable number of observations and experiments which are of in-

terest, have been made to elucidate the respiratory cardiac variations. The fact that there is an inspiratory quickening of the heart rate and an expiratory slowing is interesting and not understood. It has been suggested upon the basis of experimental work that these respiratory variations are the result of vagus impulses and that the respiratory types of arrhythmias which are observed in children, in nervous persons, and in convalescence from acute infectious diseases, are the result of a "certain lability of the vagus center." Such phenomena are, however, observed in perfectly healthy individuals (Putzig) who should possess, then, particularly "labile vagus centers." These so-called "vagus arrhythmias" (Pongs) form a cumbersome group. It includes the sinus arrhythmias of the respiratory type, the arrhythmia infantilis, those which appear during convalescence from infectious diseases. Tabora calls them the nervous arrhythmias. These respiratory variations were originally conceived as being due to purely mechanical effects produced by intrathoracic pressure changes. This was in the days when nervous influences were supposed to be supreme. Experimental work however has shown that this was not the case. Later it was considered possible that they were due to reflexes from the lungs to the vagus. Experimental work has not substantiated this conception nor that which considered the variations the result of reflexes from the respiratory muscles. Following these nervous explanations have come the chemical ones. One theory was that the respiratory frequency of the pulse was dependent upon the degree of oxygenization of the blood, because during ventilation of the lungs with oxygen the expiratory slowing was absent, and when the oxygen supply ran low the slowing reappeared.

Finally since it has been shown that the cardiac variations occur in complete absence of nervous influences, recent workers have fallen back on the theory that the variations are metabolic in origin, or that they are the results of temperature changes in the blood. Peterson and Gasser showed that the products from fatigued muscles increased the forces of systole with but slight slowing of the heart beat. Mansfeld showed that CO_2 does not increase the pulse rate. Other workers also have shown, apparently, that metabolites alone do not affect the rate of the heart and pulse.

Mansfeld's work indicates that temperature increases of the blood are essential. He showed that tetanization of the musculature of animals produces increases of temperature in the right heart, and with hot salt solutions injected into the femorals an evident "heat acceleration" of the heart was produced. The worst of it is that Mansfeld guesses that there are heat nerves in the heart which act in making with the accelerators a reflex arc.

It seems that in the insistence upon the necessity of nervous impulses the investigators are making a hard thing out of an easy one. It is certainly true that nervous impulses are useful to normal function, but that does not make them absolutely essential. It must be true that they influence metabolism by changing the rates of chemical changes. But when one can sever all nervous connections and still obtain all the usual effects (which usually appear more slowly) in their normal order it becomes evident that it is not necessary to theorize about nerve fibres and nervous impulses concerning which nothing is known. And when evidence is given that temperature variations may con-

dition heart rate, an essential factor has been found that needs no nerves to help it. In infants, metabolism is very rapid; the blood reaching the right heart is warmer than that which reaches it during quiet in the adult. The heart ought to be quicker. In the adult, exercise which increases metabolism reproduces the infantile conditions and the heart is quicker. Inspiration slows the influx of blood to the heart; expiration increases it, and so quickens the pulse, and the quickening is shown in the inspiratory phase because it has not the opportunity to produce itself sooner.

These remarks are not intended to eliminate the nerves. In the neurotic individual it is entirely probable that impulses reach the heart by way of the nerves and that depending upon which group is affected, the heart is slowed or quickened, by which we mean that the metabolism of the myocardium is increased or decreased. During such a process heat must be produced even though it is not appreciable. We know that very slight temperature changes modify deeply the changes in chemical solutions, and particularly in colloids. One would say then that the pulse rate variations are the results of metabolic changes in the myocardium which are brought about by temperature changes, and that these result from increased chemical activity in other parts of the body when heat enough is produced to cause the myocardial change, or in the heart itself, through the influence of the nerves, which increase (accelerators); or decrease (vagus) the rapidity of the chemical changes.

It is significant that Laurens reached the conclusion from his experiments on Amblystoma embryos that (in those animals) the rate of the heart beat is a logarithmic function of the temperature; that the acceleration of the heart beat is greater for lower temperatures than for higher; and that Van't Hoff's law for the velocity of chemical reactions in relation to temperature holds for the heart beat. For the present, these results of Laurens are of greater significance than those of Martin, Gruber and Lanman, which lead them to the conclusion that (in humans) the pulse rate was not dependent upon the temperature.

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—*P. G. W.*

The Function of the Spleen

IN speaking of the function of the spleen, one may recall the story of the German professor and the American student. The professor asked a member of his class to tell him what the function of the spleen was. The student, after some cogitation, said that he was sorry; he had known, but that he had forgotten. At which the professor threw up his hands and said: "Gott! only one man has known this, and he has forgotten!"

The correct conception of the role of the spleen is that it is in part a filter

for the blood, and in part a graveyard and reduction plant for the red blood cells. In it senile or dead red cells are filtered out, held and made use of by processes in splitting which free and modify the materials of which these cells are composed, sending part to the liver to be used as bile, and part to the bone marrow to be used in blood building. That this function is not an important one may be surmised from the results of splenectomy.

In a recent article, Asher and Ebnöther[1] report some experimental work which seems to have an important bearing upon the function of the spleen. They showed, first of all, that liver extracts have a decided hemolytic action, and that splenic extracts, though they may act hemolytically, do not act constantly or strongly in this way. But they also showed that by mixing liver and spleen extracts, hemolysis was far more active than it ever is in the absence of the splenic constituents. Whatever material is the active one is thermolabile and is not soluble in alcohol or ether. It is, they suggest, "either a ferment or a colloidal substance."

Their experiments with hemoglobin solutions show that in their action upon this substance, the organ extracts behave as they do toward red cells, that is, spleen extracts augment the lytic action of liver extracts, and that only spleen extracts will act in this way. Other organ extracts are inactive. Moreover, during the process of lysis (or rhexis) of hemoglobin, the process does not go to the extent of freeing the iron,—hemin is not obtained. The authors call attention to the fact that they have discovered another very interesting example of organic dependence or tissue correlation.

This work, if it be established, has a very useful practical clinical bearing. Heretofore splenectomy has been an experiment. It has been done as a last resort. But if in certain anæmic conditions it can be shown that abnormal hemolysis is fundamental, and that the anæmia is due to it rather than to a lack of production of blood cells or pigment, then it will be logical and not merely empirical to remove the organ which furnishes the normal augmenter of hemolysis. In such cases it may be that the liver itself is primarily over-active, or that the spleen is over-producing its augmenting substance.

Another indication of a very useful function of the spleen is to be found in an article of Launoy and Lévy-Bruhl.[2] These writers point out that in the case of infection with spirochæta gallinarum, splenectomy increases the grade of septicæmia but reduces the severity of the disease in that the toxic symptoms are much less marked than in other normal animals. Evidently the spleen is (in this disease at least) a very useful filter, but at the same time it is also a very active culture tube in which toxins are produced. It may perhaps be found that other infectious diseases depend for their severe symptoms upon this function of the spleen. The opposite point of view has been emphasized by Bardach, who found that splenectomized dogs were much less resistant to anthrax than normal ones. Bradford and Plimmer found that splenectomized animals inoculated with Trypanosoma brucei, died more quickly than others.

[1]Asher and Ebnöther: Zentralb. f. Physiol., 1915 (30) 61-64.
[2]Ann. Inst. Pasteur., 1915 (29) 213.

—*P. G. W.*

Lesions of the Pancreas in Diabetes

THERE is, as Labbé, Laignel-Lavastine and Vitry[1] say, scarcely another question concerning which more controversy exists than that relating to the relationships of diabetes and anatomic changes in the pancreas.

Previous to the present era of discussion which began with Lancereaux in 1877, many writers had noted the presence of pancreatic lesions in cases of diabetes, and after this time, even to the present, lesions of the abdominal salivary gland are sought for in all cases in which death has occurred in the course of the clinical complex known as diabetes mellitus. The period of experimental work on pancreatic diabetes really commenced with Mering and Minkovski who produced the essential features of the disease by removing the pancreas. From this time the reports of histologic lesions in the pancreas began to be looked upon as an essential of the disease.

But at the same time, histologic studies of the pancreas in other clinical conditions than diabetes, in which there was no abnormal secretion of sugar, began to be made which gave evidence that the lesions commonly associated with diabetes were also present. Chronic interstitial pancreatis involving the pancreas as a whole, only the tissue of the external secreting part of the gland, or only the islands, has been found associated with the most various conditions. In biliary lithiasis the most diverse lesions of the pancreas may exist, but sclerosis is the predominating one, existing in 80 of 100 cases (Mayo Robson). Weichselbaum has said that the use of alcohol predisposes to chronic pancreatitis. Chabrol has observed the same disposition in cardiac conditions. As a matter of fact, the most various factors have been reported as the causes of pancreatic changes. And nevertheless in very many instances, no matter what the type of lesion, glycosuria has been absent. In Schmidt's series of cases of diabetes, on the other hand, he found a normal pancreas in each of 8 cases, and in the majority of the other fifteen, there was so little change as to seem insufficient to account for the symptoms. Many writers, among them Hansemann, have only exceptionally found insular lesions in diabetes, though Opie and others considered insular lesions more or less essential. (It is of course to be remembered that the pancreas tissue may be abnormal in its response without showing any gross or microscopic lesion.) Hansemann considers the diffuse sclerosis which is analogous to that of the small red kidney, the essential diabetic pancreatic lesion.

Certain writers (Laguesse, Curtis, Gelle) believe that it is impossible to separate the insular lesions from the acinar ones, for, they say, histology seems to show that there is a continual transition from acini to islands and from islands to acini and that lesions involving the one should affect the other. As a matter of fact, the sections of pancreas made from post mortem tissues in the Cincinnati General Hospital, show as a rule diffuse changes rather than ones localized in one or another part of the glands.

Labbé, Laiguel-Lavastine and Vitry have for several years made a histologic study of the pancreas tissue obtained from thirty-seven individuals who died of very diverse affections, and from nineteen who died of diabetes. In

[1]Archives de med. exper., et d'anat. pathol., 1914 (26) 366.

both groups the same lesions were observed and so, it appears, the mere presence of certain types of histologic changes does not indicate the presence of diabetes; in other words, there is no pathognomonic pancreatic lesion in that disease. —*P. G. W.*

Cardiac Murmurs

ONE sometimes observes the tendency in some practitioners to overemphasize the importance of cardiac murmurs. One more frequently observes the enthusiasm with which a student seizes upon a murmur at one of the cardiac valves as the one clinical fact upon which he proceeds to rest a diagnosis. And yet it may be that the murmur is the least important expression of physical deficiency. Cardiac murmurs have an essential value only when the whole cardio-vascular system is considered, and often only when the whole corporeal system of the individual is taken into account. Such remarks apply not only to murmurs but also to many other cardiac phenomena. It is therefore useful when a writer of experience calls attention to the fallacies of judging a patient by an isolated clinical phenomenon. Parsons-Smith,[1] for instance, says that murmurs must be investigated with care, in making interpretations from them, because a heart in which a murmur occurs may be a perfectly efficient one, and suited to the individual for whom it works. Also the amount of damage in a heart cannot be deduced from a study of the murmur alone. It is what a heart does, not what it sounds like, that indicates its value,—its strength or weakness. If at the end of a period of reasonable physical strain (or mental?) the heart has lost no tone,—shows no dilatation, it is a functionally good heart no matter how it whistles or blows. If it loses tone then it is not functionally fit, no matter if no abnormal sounds are heard. Changes in the size of a heart after exertion may be decided in many cases by use of the X-ray plate or, better, the fluoroscope.

[1]The Practitioner, 1915 (94) 533.

—*P. G. W.*